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Ufficio G2

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N. MI2003 A 001378

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Roma, lì 18 MAG. 2004

IL FUNZIONARIO

Dr.ssa Paola Giuliano

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4329PTIT

AL MINISTERO DELLE ATTIVITÀ PRODUTTIVE
UFFICIO ITALIANO BREVETTI E MARCHI - ROMA
DOMANDA DI BREVETTO PER INVENZIONE INDUSTRIALE, DEPOSITO RISERVE, ANTICIPATA ACCESSIBILITÀ AL PUBBLICO

MODULO A

A. RICHIEDENTE (I)

1) Denominazione: GLAXOSMITHKLINE S.p.A.
Residenza: VERONA

2) Denominazione: codice: 00212840235
Residenza:

B. RAPPRESENTANTE DEL RICHIEDENTE PRESSO L'U.I.B.M. codice:

cognome nome: Dr.ssa Gemma Gervasi ed altri
denominazione studio di appartenenza: Notarbartolo & Gervasi S.p.A. cod. fiscale:
via: C.so di Porta Vittoria n. 9 città: Milano cap: 20122 (prov): MI

C. DOMICILIO ELETTIVO destinatario:
via: n. città: cap: (prov):

D. TITOLO
classe proposta (sez/cl/scl): C07D gruppo/sottogruppo:
Nuovi ligandi indolici 3-sostituiti del recettore ORL-1

ANTICIPATA ACCESSIBILITÀ AL PUBBLICO: SI ☐ NO ☒ SE ISTANZA: DATA: N° PROTOCOLLO:

E. INVENTORI DESIGNATI
cognome nome
1) FARINA Carlo
2) RONZONI Silvano
3) VALLESE Stefania
4) CONSONNI Alessandra

F. PRIORITÀ

	nazione o organizzazione	tipo di priorità	numero di domanda	data di deposito	allegato S/R
1)	nessuna				
2)					

SCIOGLIMENTO RISERVE — Data / N° Protocollo

G. CENTRO ABILITATO DI RACCOLTA COLTURE DI MICRORGANISMI, denominazione:

H. ANNOTAZIONI SPECIALI
nessuna

DOCUMENTAZIONE ALLEGATA

	N. es.			
Doc. 1)	1	PROV	n. pag. 56	riassunto con disegno principale, descrizione e rivendicazioni (obbligatorio 1 esemplare) ....
Doc. 2)	0	PROV	n. tav. 00	disegno (obbligatorio se citato in descrizione, 1 esemplare) .....
Doc. 3)	1	RIS		lettera d'incarico, procura o riferimento procura generale .....
Doc. 4)	0	RIS		designazione inventore .....
Doc. 5)	0	RIS		documenti di priorità con traduzione in italiano .....
Doc. 6)	0	RIS		autorizzazione o atto di cessione .....
Doc. 7)	0			nominativo completo del richiedente

SCIOGLIMENTO RISERVE — Data / N° Protocollo
confronta singole priorità

8) attestati di versamento, totale Euro: Duecentonovantuno/80.= + Centoottanta/76.=

COMPILATO IL 04/07/2003 **FIRMA DEL(I) RICHIEDENTE(I)** Gemma Gervasi obbligatorio

CONTINUA SI/NO NO

DEL PRESENTE ATTO SI RICHIEDE COPIA AUTENTICA SI/NO SI

CAMERA DI COMMERCIO IND. ART. E AGR. DI MILANO MILANO

VERBALE DI DEPOSITO NUMERO DI DOMANDA MI2003A 001378 Reg. A. codice 15

L'anno DUEMILATRE il giorno QUATTRO del mese di LUGLIO

Il(i) richiedente(i) sopraindicato(i) ha(hanno) presentato a me sottoscritto la presente domanda, corredata di n. 00 fogli aggiuntivi per la concessione del brevetto sopraripportato.

I. ANNOTAZIONI VARIE DELL'UFFICIALE ROGANTE

IL DEPOSITANTE

L'UFFICIALE ROGANTE

RIASSUNTO INVENZIONE CON DISEGNO PRINCIPALE, DESCRIZIONE E RIVENDICAZIONE

PROSPETTO A

NUMERO DOMANDA MI2003A001578 REG. A

NUMERO BREVETTO

DATA DI DEPOSITO 04/07/2003

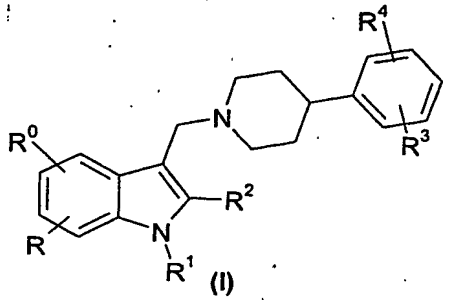
DATA DI RILASCIO

D. TITOLO

Nuovi ligandi indolici 3-sostituiti del recettore ORL-1

L. RIASSUNTO

Si descrivono nuovi ligandi del recettore ORL-1, utili per modulare l'attivita' di detti recettori in un paziente che ne necessita, e per prevenire e trattare malattie dipendenti dalla stimolazione di questo recettore. I nuovi composti rispondono dalla formula strutturale (I)



(I)

M. DISEGNO

Notarbartolo & Gervasi S.p.A.

Domanda di brevetto per invenzione industriale dal titolo:

"NUOVI LIGANDI INDOLICI 3-SOSTITUITI DEL RECETTORE ORL-1"

a nome di: GLAXOSMITHKLINE S.p.A.

con sede in: VERONA

Inventori designati : FARINA Carlo, RONZONI Silvano, VALLESE Stefania, CONSONNI Alessandra

MI 2003 A 001378

depositata il

con n.

* * * * *

La presente invenzione si riferisce a certi nuovi composti, a processi per prepararli, a composizioni farmaceutiche che li contengono, e all'uso di tali composti in medicina. L'invenzione si riferisce in particolare ad un gruppo di nuovi composti dotati di attività antagonista o agonista dei recettori ORL-1 ed utili nel trattamento delle malattie legate ad una modulazione di tali recettori.

Il recettore ORL-1 si trova localizzato lungo tutto l'asse nervoso ed è coinvolto in diversi fenomeni patologici, tra cui la trasmissione del dolore. Sono noti diversi ligandi peptidici e non peptidici del recettore ORL-1; tra i ligandi non peptidici sono noti composti con struttura morfinanica, benzimidazopiperidinica, spiropiperidinica, arilpiperidinica, 4-amminochinolinica (*Life Sciences*, 73, **2003**, 663-678); WO0183454 e WO 03040099 descrivono altri antagonisti ORL-1 a struttura benzosuberonilpiperidinica sostituita in posizione 5 con un gruppo idrossi, alcossi, ammino o alchilammino, ed il loro metodo di sintesi. *J.Med.Chem.*, 1997, 40(23), 3912-14 e WO 9709308 descrivono certi indoli sostituiti in posizione 3 con un gruppo bipiperazinico, come

antagonisti del recettore NPY-1.

J.Med.Chem., 1996, 39(10), 1941-2, WO 9424105 , WO 9410145, WO 02241894, WO9629330 e GB 2076810 descrivono vari 3-piperazinilmetil indoli variamente sostituiti, come ligandi dei recettori dopaminici, in particolare del recettore D4.

GB 2083476 descrive specifici 3-arilpiperidinilmetil indoli con azione inibitrice dell'uptake della 5-HT.

US 5215989 descrive certi derivati disubstituiti piperazinici ed imidazolici utili come agenti antiaritmici di classe III.

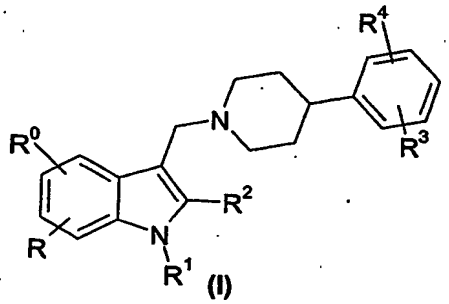
EP 846683 descrive derivati idrossipiperidinici come bloccanti del recettore NMDA.

E' stato ora trovato che certi 3-amminometilindoli sono potenti ligandi del recettore ORL-1, e quindi possono essere utili come analgesici nell'uomo o nell'animale per il trattamento, ad esempio, del dolore acuto; dolore cronico neuropatico o infiammatorio, includendo la neuralgia postherpetica, neuralgia, neuropatia diabetica e dolore post-infartuale; dolore viscerale incluso quello associato alla sindrome da colon irritabile, dismenorrea, ed iperriflessia della vescica; osteoartrite, dolore alla schiena, travaglio doloroso in gravidanza e terapia della tolleranza e dipendenza da oppioidi.

Questi composti possono quindi possono essere utili nel trattamento o profilassi di disordini alimentari, quali l'anoressia e bulimia; ansietà e condizioni di stress; disordini gastrointestinali inclusa la sindrome da colon irritabile, e sintomi associati con dispepsia non ulcerosa e riflusso gastroesofageo; malattie del sistema immunitario; disfunzioni del

sistema cardiovascolare; perdita di memoria, disordini cognitivi, danni motori e neurodegenerazione dovuta a malattia di Alzheimer; demenza senile, malattia di Parkinson o altre patologie neurodegenerative; infarto; epilessia; diuresi alterata e escrezione di sodio; sindrome di inappropriata secrezione di ormone antidiuretico (SIADH); sindrome adulta da stress respiratorio (ARDS); insufficienza cardiaca congestizia; cirrosi con asciti; disfunzioni sessuali tra cui l'impotenza e la frigidità; ed alterata funzione polmonare, includendo la malattia cronica da ostruzione polmonare.Questi composti possono inoltre essere utili nel trattamento o profilassi di tosse; asma; depressione; abuso di droghe come ad esempio abuso di alcol; demenze come demenza vascolare e demenza associata ad AIDS; disordini metabolici come l'obesità; patologie associate alle alterazioni della pressione arteriosa, e per omeostasi idrica ed escrezione di sodio.

I composti dell'invenzione rispondono alla formula strutturale (I)



(I)

dove:

R e R^0 sono ciascuno indipendentemente idrogeno, alogeno, C_{1-6}alchile, peraloC_{1-6}alchile, C_{1-6}alcossi, idrossi, ammino, C_{1-6}alchilammino, di(C_{1-6}alchil)ammino, amminoC_{1-6}alchile, (C_{1-6}alchil)amminoC_{1-6}alchile, di(C_{1-}

$_6$alchil)amminoC$_{1-6}$alchile, arile.

R^1 è idrogeno, C$_{1-6}$alchile, C$_{3-6}$alchenil, C$_{3-6}$alchinil, arilC$_{1-6}$alchile, eteroarilC$_{1-6}$alchile, (C$_{3-7}$cicloalchil)alchile, amminoC$_{1-6}$alchile, (C$_{1-6}$alchil)amminoC$_{1-6}$alchile, di(C$_{1-6}$alchil)amminoC$_{1-6}$alchile, idrossiC$_{1-6}$alchile, C$_{1-6}$alcossiC$_{1-6}$alchile, arilossiC$_{1-6}$alchile, COarile, SO$_2$arile dove ciascun arile o eteroarile può essere sostituito una o più volte da alogeno, C$_{1-6}$alcossi, C$_{1-6}$alchile, idrossi, ammino, C$_{1-6}$alchilammino, di(C$_{1-6}$alchil)ammino, amminoC$_{1-6}$alchile, (C$_{1-6}$alchil)amminoC$_{1-6}$alchile, di(C$_{1-6}$alchil)amminoC$_{1-6}$alchile, arile o peraloC$_{1-6}$alchile.

R^2 è C$_{3-7}$cicloalchile, arile, eteroarile, arilC$_{1-6}$alchile, eteroarilC$_{1-6}$alchile, dove ciascun arile o eteroarile può essere sostituito una o più volte da alogeno, C$_{1-6}$alcossi, C$_{1-6}$alchile, idrossi, ammino, C$_{1-6}$alchilammino, di(C$_{1-6}$alchil)ammino, amminoC$_{1-6}$alchile, (C$_{1-6}$alchil)amminoC$_{1-6}$alchile, di(C$_{1-6}$alchil)amminoC$_{1-6}$alchile, arile o peraloC$_{1-6}$alchile.

R^3 e R^4 sono ciascuno indipendentemente idrogeno, alogeno, C$_{1-6}$alchile, peraloC$_{1-6}$alchile, C$_{1-6}$alcossi, idrossi, ammino, C$_{1-6}$alchilammino, di(C$_{1-6}$alchil)ammino, amminoC$_{1-6}$alchile, (C$_{1-6}$alchil)amminoC$_{1-6}$alchile, di(C$_{1-6}$alchil)amminoC$_{1-6}$alchile, arile.

I composti di formula (I) possono esibire stereoisomeria a causa della presenza di atomi chirali e/o legami multipli. La presente invenzione quindi si estende agli stereoisomeri dei composti di formula (I), includendo i racemi, gli enantiomeri, i diastereoisomeri, e gli isomeri geometrici.

E' stato trovato che, dove un composto di formula (I) esibisce isomerismo ottico, un enantiomero possiede una maggiore affinità per il

recettore ORL-1 rispetto al suo antipodo.

Pertanto, la presente invenzione fornisce anche un enantiomero di un composto di formula (I).

In un ulteriore aspetto, la presente invenzione fornisce una miscela di enantiomeri di un composto di formula (I) dove un enantiomero è presente in una proporzione maggiore rispetto al suo antipodo.

Come precedentemente citato, i composti di formula (I) sono ligandi del recettore ORL-1. Quindi, si fornisce un composto di formula (I) come sostanza terapeutica attiva.

Secondo un altro aspetto della presente invenzione si fornisce un metodo di modulare l'attività del recettore ORL-1 in un paziente umano o animale che lo necessita, comprendente la somministrazione al paziente umano o animale di un quantitativo efficace di un composto di formula (I).

In un altro aspetto della presente invenzione, si fornisce l'uso di un composto di formula (I) nella preparazione di un medicamento per somministrazione umana o animale, ultile per modulare l'attività del recettore ORL-1.

Detti composti di formula I possono essere agonisti o antagonisti del recettore ORL-1.

Secondo un particolare aspetto della presente invenzione, un antagonista di formula (I) può essere usato come analgesico negli umani o negli animali per il trattamento, ad esempio del dolore acuto; dolore cronico neuropatico o inflammatorio, includendo la neuralgia postherpetica, neuralgia, neuropatia diabetica e dolore post-infartuale;

dolore viscerale incluso quello associato alla sindrome da colon irritabile, dismenorrea, ed iperriflessia della vescica, osteoartrite, dolore alla schiena, travaglio doloroso in gravidanza e terapia della tolleranza e dipendenza da oppioidi.

Secondo un ulteriore aspetto dell' invenzione, i composti di formula (I) possono essere usati nel trattamento o profilassi di disordini alimentari, quali l'anoressia e bulimia; ansietà e condizioni di stress; disordini gastrointestinali inclusa la sindrome da colon irritabile, e sintomi associati con dispepsia non ulcerosa e riflusso gastroesofageo; malattie del sistema immunitario; disfunzioni del sistema cardiovascolare; perdita di memoria, disordini cognitivi, danni motori e neurodegenerazione dovuta a malattia di Alzheimer; demenza senile, malattia di Parkinson o altre patologie neurodegenerative; infarto; epilessia; diuresi alterata e escrezione di sodio; sindrome di inappropriata secrezione di ormone antidiuretico (SIADH); sindrome adulta da stress respiratorio (ARDS); insufficienza cardiaca congestizia; cirrosi con asciti; disfunzioni sessuali tra cui l'impotenza e la frigidità; ed alterata funzione polmonare, includendo la malattia cronica da ostruzione polmonare. Questi composti possono inoltre essere utili nel trattamento o profilassi di tosse; asma; depressione; abuso di droghe come ad esempio abuso di alcol; demenze come demenza vascolare e demenza associata ad AIDS; disordini metabolici come l'obesità; patologie associate alle alterazioni della pressione arteriosa, e per omeostasi idrica ed escrezione di sodio.

I composti dell'invenzione sono quindi utili nella terapia e profilassi di

tutte le malattie dipendenti dalla modulazione del recettore ORL-1, quali quelle sopra esemplificate.

Nella suddetta formula (I),

R ed R^0 sono preferibilmente, idrogeno, alogeno, C_{1-6}alchile, C_{1-6}alcossi; più preferibilmente, R ed R^0 sono idrogeno, cloro, fluoro, metile, metossi.

R^1 è preferibilmente idrogeno, C_{1-6}alchile, C_{3-6}alchenil, C_{3-6}alchinil, arilC_{1-6}alchile, (C_{3-7}cicloalchil)alchile, idrossiC_{1-6}alchile, CO-arile, SO_2-arile; più preferibilmente, R^1 è idrogeno, metile, n-propile, isopentile, allile, 2-idrossietile, ciclopropilmetile, cicloesilmetile, benzile, fluorobenzile, clorobenzile, bromobenzile, metossibenzile, metilbenzile, *t*-butilbenzile, trifluorometilbenzile, bifenilmetile, fenossietile, 2-naftilmetile, benzoile, benzensolfonile.

R^2 è preferibilmente arile, eteroarile, arilC_{1-6}alchile; più preferibilmente, R^2 è fenile, clorofenile, metossifenile, fluorofenile, 2-furile, 2-tienile, 2-piridile, benzile.

R^3 e R^4 sono preferibilmente idrogeno, alogeno, C_{1-6}alchile, peraloC_{1-6}alchile, C_{1-6}alcossi; più preferibilmente, R^3 e R^4 sono idrogeno, cloro, fluoro, bromo, metile, metossi, trifluorometile.

Il termine "arile" qui utilizzato include i gruppi C_{5-10} arile, in particolare fenile e naftile. I gruppi C_{1-6} alchile possono essere lineari o ramificati e sono preferibilmente gruppi C_{1-2} alchile, più preferibilmente metile. Il termine "alogeno" include i gruppi iodo, cloro, bromo, e fluoro, specialmente cloro, fluoro e bromo.Il termine "eteroarile" include anelli eterociclici saturi ed insaturi.

Specifici composti di formula (I) secondo la presente invenzione (di

ciascuno dei quali si intendono anche i corrispondenti sali quali ad esempio cloridrato o trifluoroacetato), sono i seguenti:

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-metil-1H-indolo;

2-(4-cloro-fenil)-3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-fenil-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

2-fenil-3-(4-fenil-piperidin-1-ilmetil)-1H-indolo;

2-(2-cloro-fenil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-(2-cloro-fenil)-3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-(2-cloro-fenil)-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-(2-cloro-fenil)-3-(4-fenil-piperidin-1-ilmetil)-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-(2-metossi-fenil)-1H-indolo;

3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-2-(2-metossi-fenil)-1H-indolo;

2-(2-metossi-fenil)-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-(2-metossi-fenil)-3-(4-fenil-piperidin-1-ilmetil)-1H-indolo;

3-[4-(2,6-diclorofenil)-piperidin-1-ilmetil]-2-(3-metossi-fenil)-1H-indolo;

3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-2-(3-metossi-fenil)-1H-indolo;

2-(3-metossi-fenil)-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-(3-metossi-fenil)-3-(4-fenil-piperidin-1-ilmetil)-1H-indolo;

2-(4-cloro-fenil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-(4-cloro-fenil)-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-(4-cloro-fenil)-3-(4-fenil-piperidin-1-ilmetil)-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-(4-fluoro-fenil)-1H-indolo;

3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-2-(4-fluoro-fenil)-1H-indolo;

2-(4-fluoro-fenil)-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-(4-fluoro-fenil)-3-(4-fenil-piperidin-1-ilmetil)-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-furan-2-il-1H-indolo;

3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-2-furan-2-il-1H-indolo;

2-furan-2-il-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-furan-2-il-3-(4-fenil-piperidin-1-ilmetil)-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-piridin-2-il-1H-indolo;

3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-2-piridin-2-il-1H-indolo;

2-piridin-2-il-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

3-(4-fenil-piperidin-1-ilmetil)-2-piridin-2-il-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-tiofen-2-il-1H-indolo;

3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-2-tiofen-2-il-1H-indolo;

2-tiofen-2-il-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

3-(4-fenil-piperidin-1-ilmetil)-2-tiofen-2-il-1H-indolo;

2-benzil-3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-benzil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1H-indolo;

3-[4-(4-metossi-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2-fluoro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(3-fluoro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(4-fluoro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

2-fenil-3-[4-(4-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

3-[4-(2-cloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(3-cloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(4-cloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

2-fenil-3-(4-o-tolil-piperidin-1-ilmetil)-1H-indolo;

3-[4-(2,3-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2-bromo-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2,5-dimetil-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2,6-difluoro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(3-bromo-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2-metossi-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

1-benzil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1-propil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-metil-2-fenil-1H-indolo;

3-(4-(2,6-dicloro-fenil)piperidin-1-ilmetil)-1-(2-idrossietil)-2-fenil-1H-indolo;

1-(4-*tert*-butil-benzil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(3-metil-butil)-2-fenil-1H-indolo;

1-ciclopropilmetil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(3-metossi-benzil)-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(2-metil-benzil)-2-fenil-1H-indolo;

1-cicloesilmetil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-

indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(4-metil-benzil)-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(4-fluoro-benzil)-2-fenil-1H-indolo;

1-(3-cloro-benzil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

1-(2-cloro-benzil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

1-(4-Cloro-benzil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

1-allil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1-prop-2-inil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(2-metossi-benzil)-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(4-metossi-benzil)-2-fenil-1H-indolo;

1-(4-bromo-benzil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

1-bifenil-4-ilmetil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-naftalen-2-ilmetil-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(2-fenossi-etil)-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(3-metil-benzil)-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(2-fluoro-benzil)-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(3-fluoro-benzil)-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1-(2-trifluorometil-benzil)-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1-(3-trifluorometil-benzil)-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1-(4-trifluorometil-benzil)-1H-indolo;

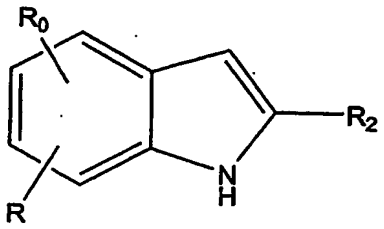
1-benzensolfonil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

1-benzoil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo.

L'invenzione riguarda anche l'impiego terapeutico di un gruppo di composti di formula (IA): tale formula è uguale alla formula (I), con la sola differenza che i significati previsti per il gruppo R2 includono anche l'idrogeno e il C_{1-6} alchile.

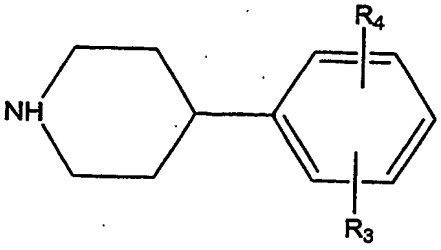
La presente invenzione fornisce anche i procedimenti per preparare i composti di formula (I).

I composti di formula (I) in cui **R1 è idrogeno**, possono essere ottenuti come segue: un composto di formula (II)



(II)

in cui R, R0 ed R2 hanno i significati dati per la formula (I), viene funzionalizzato in posizione 3 mediante reazione con formaldeide ed un composto di formula (III)

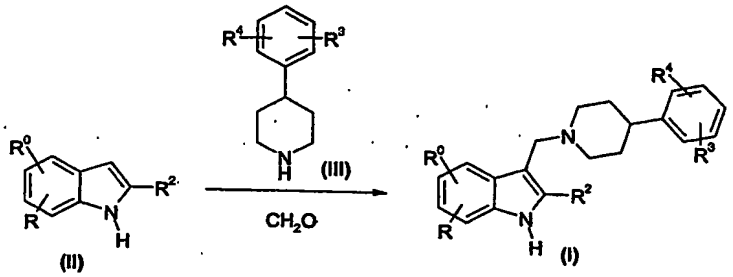


(III)

dove R3 ed R4 sono come definiti per la formula (I), ottenendo così i composti di formula (I) in cui R1 è idrogeno.

La reazione di funzionalizzazione è preferibilmente una reazione di Mannich, come descritta in testi di riferimento standard di metodologie sintetiche quali *J. March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience*. In particolare, i composti di formula (I) possono venire preparati secondo lo schema 1, a partire dai composti di formula (II), formaldeide ed ammine di formula (III).

Schema 1



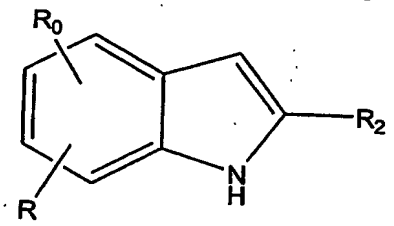
In una procedura tipica, un'ammina di formula (III) viene discolta in un adatto solvente come, per esempio, metanolo o diossano o una miscela di entrambi, e a questa soluzione si aggiungono formaldeide acquosa ed acido acetico. Dopo un opportuno periodo di tempo, tipicamente tra 5 min ed 1 h, si aggiunge alla precedente soluzione una soluzione di un indolo di formula (II) in un opportuno solvente, come ad esempio metanolo o diossano o una miscela di entrambi, mantenendo la temperatura della soluzione risultante generalmente compresa tra 0°C e temperatura ambiente. La miscela di reazione viene agitata per un adatto periodo di tempo, tipicamente tra 1 h e 20 h, quindi lavorata secondo metodi noti. Due procedure preferite di lavorazione sono qui indicate come procedura A e procedura B.

Nella procedura A, si aggiunge acqua alla miscela di reazione, seguita da una soluzione di un'opportuna base, come idrossido di ammonio acquoso, fino a pH basico, quindi si estrae con un adatto solvente organico come ad esempio acetato di etile. La fase organica viene raccolta e anidrificata con, ad esempio, sodio solfato, ed il solvente viene rimosso per evaporazione. Il prodotto grezzo può essere

purificato, se necessario, con metodi convenzionali di purificazione come cromatografia flash, triturazione, cristallizzazione e HPLC preparativa.

Nella procedura B, la miscela di reazione viene versata su una cartuccia di resina acida ed eluita con un adatto solvente, come ad esempio diclorometano o metanolo, per rimuovere impurità non-basiche, e quindi con una soluzione di una opportuna base in un adatto solvente organico come, ad esempio, una soluzione metanolica di ammoniaca, per recuperare il composto desiderato di formula (I). Il solvente viene rimosso per evaporazione ed il prodotto grezzo può essere purificato, se necessario, con metodi convenzionali di purificazione come cromatografia flash, triturazione, cristallizzazione e HPLC preparativa.

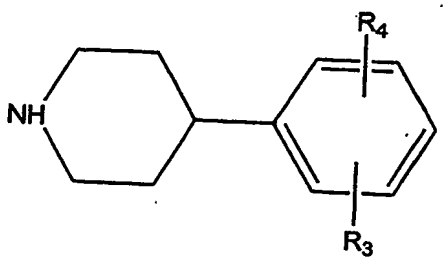
I composti di formula (I) in cui **R1 è diverso da idrogeno**, possono essere ottenuti come segue: un composto di formula (II)



(II)

in cui R, R0 ed R2 hanno i significati dati per la formula (I), viene trattato secondo i due passaggi seguenti, che possono aver luogo in qualsiasi ordine:

(a): reazione con formaldeide ed un composto di formula (III)



(III)

dove R3 ed R4 sono come definiti per la formula (I),

(b) reazione con un composto di formula R1-X, in cui R1 è come definito in formula (I) ed X è un adatto gruppo uscente,

ottenendo così i composti di formula (I).

Nel caso si eseguano i passaggi nell'ordine (a) → (b), il composto di formula (II) viene prima funzionalizzato in posizione 3 mediante reazione con formaldeide ed il composto di formula (III); l'intermedio 3-funzionalizzato così ottenuto viene quindi N-alchilato in posizione 1 sull'anello indolico, mediante trattamento con il composto R1-X, ottenendo il composto finale di formula (I).

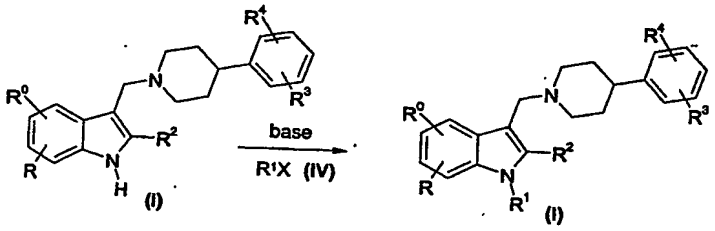
Nel caso si eseguano i passaggi nell'ordine inverso (b) → (a), il composto di formula (II) viene prima N-alchilato in posizione 1 sull'anello indolico, mediante reazione con il composto R1-X; l'intermedio N-alchilato così ottenuto viene quindi 3-funzionalizzato mediante reazione con formaldeide ed il composto di formula (III), ottenendo il composto finale di formula (I).

Il passaggio (a) (3-funzionalizzazione) viene effettuato preferibilmente mediante reazione di Mannich, nelle modalità precedentemente dettagliate.

Il passaggio (b), è una reazione di sostituzione nucleofila che può essere effettuato secondo modalità comunemente note; in particolare

viene effettuata facendo reagire con una base forte il composto di formula (II) (oppure, come illustrato nello schema 2 qui sotto, il suo derivato 3-sostituito risultante dal passaggio (a)) e quindi trattando il risultante anione indolile con un adatto agente alchilante/acilante, di formula (IV);

Schema 2



In una procedura tipica, un'opportuna base come, ad esempio sodio idruro, viene aggiunta sotto atmosfera inerte, tipicamente di argo o azoto, ad una soluzione di un composto di formula (I) in un adatto solvente anidro, come ad esempio dimetilformammide, ad un'adatta temperatura, tipicamente tra 0°C e temperatura ambiente. Dopo un opportuno periodo di tempo, tipicamente tra 15 min e 1 h, un opportuno alchil o acil alogenuro di formula (IV) viene aggiunto alla miscela di reazione, o tal quale o disciolto in un adatto solvente anidro come ad esempio dimetilformammide; se necessario, ulteriori aggiunte di alchil o acil alogenuro possono essere effettuate. La miscela di reazione risultante viene agitata ad un'adatta temperatura, tipicamente temperatura ambiente, per un opportuno periodo di tempo, tipicamente nell'intervallo tra 1 h e 20 h. La lavorazione può venire effettuata

secondo metodi noti. Due procedure preferite di lavorazione sono qui indicate come procedura A o procedura B.

Nella procedura A, si aggiunge acqua alla miscela di reazione, che viene quindi estratta con un adatto solvente organico come ad esempio dietiletere. La fase organica viene raccolta ed anidrificata con ad esempio sodio solfato, ed il solvente viene rimosso per evaporazione. Il prodotto grezzo può essere purificato, se necessario, con metodi convenzionali di purificazione come cromatografia flash, triturazione, cristallizzazione e HPLC preparativa.

Nella procedura di lavorazione B, si aggiunge acqua alla miscela di reazione, e quindi si filtra attraverso un opportuno filtro a ritenzione d'acqua, eluendo con un adatto solvente come ad esempio acetato di etile. La soluzione risultante può venire concentrata, se necessario, e quindi versata su una cartuccia di resina acida ed eluita con un adatto solvente, come ad esempio, metanolo, per rimuovere impurezze non-basiche, e quindi con una soluzione di un'opportuna base in un adatto solvente organico come ad esempio una soluzione metanolica di ammoniaca, per recuperare il composto desiderato di formula (I). Il solvente vene rimosso per evaporazione ed il prodotto grezzo può essere purificato, se necessario, con metodi convenzionali di purificazione come cromatografia flash, triturazione, cristallizzazione e HPLC preparativa.

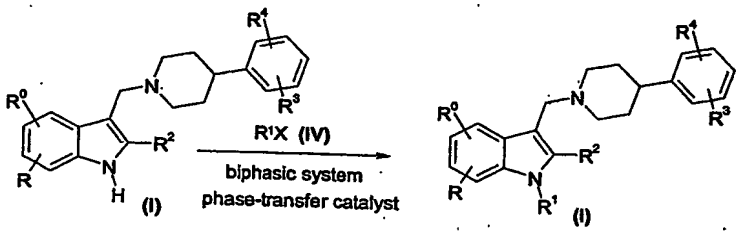
I composti di formula (II) sono noti o commercialmente disponibili, o possono essere preparati secondo procedure descritte in testi di riferimento standard di metodologie sintetiche, come *J. March,*

Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience.

I composti di formula (III) sono conosciuti o commercialmente disponibili, o possono essere preparati mediante le procedure descritte in WO 01/83454.

Alternativamente, il passaggio (b) può essere realizzato facendo reagire il composto di formula (II) (oppure, come illustrato nello schema 3, il suo derivato 3-sostituito risultante dal passaggio (a)) con un adatto agente alchilante/acilante di formula (IV), in condizioni di trasferimento di fase, come descritto ad esempio in *W.E. Keller, Phase-Transfer Reactions, Vols. 1 e 2, 1986, Georg Thieme Verlag.*

Schema 3



In una procedura tipica, un composto di formula (I) viene disciolto in un adatto sistema bifasico, tipicamente una miscela 1:1 di toluene e soluzione acquosa di sodio idrossido; si aggiunge quindi un adatto catalizzatore di trasferimento di fase, come ad esempio Aliquat® 336. Dopo un opportuno periodo di tempo, tipicamente compreso tra 10 min ed 1 h, si aggiunge un adatto alchil- o acil alogenuro di formula (IV) alla miscela di reazione; se necessario, ulteriori aggiunte di alchil- o acil-alogenuro possono essere effettuate. La miscela di reazione viene agitata vigorosamente ad un'adatta temperatura, tipicamente

temperatura ambiente, per un opportuno periodo di tempo, tipicamente da 5 h a 20 h, quindi filtrata attraverso un adatto filtro a ritenzione d'acqua, eluendo con un adatto solvente come ad esempio etil acetato. Il solvente viene rimosso per evaporazione ed il prodotto grezzo può essere purificato, se necessario, con metodi convenzionali di purificazione come cromatografia flash, triturazione, cristallizzazione e preparative HPLC.

I composti di formula (IV), ad es. alchilanti/acilanti, usati nel passaggio (b) sono noti o commercialmente disponibili, o possono essere preparati secondo procedure descritte in testi standard di riferimento di metodologie sintetiche, come *J. March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience.*

I composti di formula (I) secondo l'invenzione possono essere preparati nella forma di sali o idrati. Opportuni sali sono sali farmaceuticamente accettabili. Opportuni idrati sono idrati farmaceuticamente accettabili.

Un quantitativo efficace di composto dell'invenzione dipende da fattori quali, ad esempio, la natura e gravità della malattia/e da trattare e dal peso del paziente. In ogni caso una dose unitaria contiene normalmente da 0.1 a 50 mg, ad esempio da 0.5 a 10 mg, del composto. Dosi unitarie vengono normalmente somministrate una o più volte al giorno, ad esempio 2, 3, o 4 volte al giorno, in particolare da 1 a 3 volte al giorno, così che la dose totale giornaliera è normalmente compresa, per un adulto di 70 kg, tra 0.1 e 50 mg, ad esempio tra 0.1 e 5 mg, cioè nell'intervallo approssimativamente tra 0.001 e 1 mg/kg/giorno, in particolare tra 0.005 e 0.2 mg/kg/giorno. Per somministrazione orale o

parenterale, è altamente preferito che il composto sia somministrato in forma di composizione con dose unitaria, ad esempio in forma di composizione orale o parenterale con dose unitaria.

Tali composizioni vengono preparate per miscelazione e vengono opportunamente adattate alla somministrazione orale o parenterale, e in quanto tali, possono essere nella forma di compresse, capsule, preparazioni orali, polveri, granuli, pastiglie, polveri ricostituibili, soluzioni liquide iniettabili o infusibili, o sospensioni o supposte.

Compresse e capsule per somministrazione orale sono normalmente presentate in forma di dose unitaria, e contengono eccipienti convenzionali quali leganti, fillers, diluenti, agenti di compressazione, lubrificanti, detergenti, disintegranti, coloranti, aromi ed umidificanti. Le compresse possono essere ricoperte secondo metodi ben noti nell'arte. Adatti fillers includono cellulosa, mannitolo, lattosio e altri simili agenti. Adatti disintegranti includono amido, polivinilpirrolidone ed derivati dell'amido come amido sodio glicolato. Adatti lubrificanti includono, ad esempio, magnesio stearato. Adatti agenti umidificanti includono sodio laurilsolfato.

Queste composizioni solide orali possono essere preparate con metodi convenzionali di miscelazione, riempimento o compressione. E' possibile ripetere le operazioni di miscelazione per disperdere l'attivo in composizioni contenenti larghe quantità di fillers. Tali operazioni sono convenzionali.

Le preparazioni liquide orali possono essere nella forma di, ad esempio, sospensioni acquose o oleose, soluzioni, emulsioni, sciroppi, o elisir, o

possono essere presentate come prodotto secco per recostituzione con acqua o con adatto veicolo prima dell'uso. Tali preparazioni liquide possono contenere additivi convenzionali quali agenti sospendenti, ad esempio sorbitolo, sciroppo, metilcellulosa, gelatina, idrossietilcellulosa, carbossimetilcellulose, gel di alluminio stearato o grassi edibili idrogenati, agenti emulsionanti, ad esempio lecitina, sorbitan monooleato, o acacia; veicoli non acquosi (che possono includere oli edibili), ad esempio, olio di mandorle, olio di cocco frazionato, esteri oleosi come esteri di glicerina, glicol propilenico, o alcol etilico; conservanti, ad esempio metil o propil p-idrossibenzoato o acido sorbico, e se desiderato, aromi o coloranti convenzionali.

Le formulazioni orali includono anche formulazioni convenzionali a rilascio protratto, come compresse o granuli aventi un rivestimento enterico.

Per la somministrazione parenterale, si possono preparare unità di dosaggio fluide, contenenti il composto e un veicolo sterile. Il composto, dipendentemente dal veicolo e dalla concentrazione, può essere sospeso o disciolto. Le soluzioni parenterali sono normalmente preparate sciogliendo il composto in un veicolo e sterilizzando mediante filtro, prima di riempire opportune fiale o ampolle e sigillare. Vantaggiosamente è possibile anche sciogliere nel veicolo adiuvanti come anestetici locali, conservanti e agenti tamponanti. Per aumentare la stabilità, la composizione può venire congelata dopo aver riempito la fiala e rimosso l'acqua sotto vuoto. Le sospensioni parenterali sono preparate sostanzialmente nello stesso modo, con la differenza che il

composto può essere sospeso nel veicolo anziché disciolto, e venire sterilizzato per esposizione ad ossido di etilene prima di essere sospeso nel veicolo sterile. Vantaggiosamente, è possibile includere un tensioattivo o un umettante nella composizione per facilitare la uniforme distribuzione del composto dell'invenzione.

Come è pratica comune, le composizioni sono normalmente accompagnate da istruzioni scritte o stampate, per l'uso nel trattamento in questione.

Pertanto, in un altro aspetto della presente invenzione si fornisce anche una composizione farmaceutica comprendente un composto di formula I, o un suo sale o idrato farmaceuticamente accettabile, ed un carrier farmaceuticamente accettabile.

L'invenzione viene ora illustrata mediante i seguenti esempi non limitanti.

Esempio 1

3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo cloridrato

1.17 g (5.1 mmol) di 4-(2,6-dicloro-fenil)-piperidina vengono disciolte in 4 mL di diossano, cui si aggiungono 4 mL di acido acetico glaciale e 0.41 mL (5.1 mmol) di una soluzione acquosa al 37% di formaldeide, seguiti da una soluzione di 893 mg (4.62 mmol) di 2-fenil-1H-indolo in 8 mL di diossano. La miscela di reazione viene agitata per 3 h a temperatura ambiente, quindi si aggiunge acqua seguita da NH_4OH concentrato fino a pH basico. La miscela di reazione viene estratta con AcOEt, la fase organica viene anidrificata con Na_2SO_4 ed il solvente rimosso *in vacuo*,

ottenendo 2 g di composto grezzo. 1 g di base libera viene disciolto in CH_2Cl_2, la soluzione viene portata a pH acido con Et_2O/HCl ed il solvente viene rimosso *in vacuo*. Il solido risultante viene triturato con Et_2O, filtrato ed essiccato, ottenendo 1 g del composto finale come solido bianco.

M.p. = 169-171°C. IR (KBr, cm^{-1}) = 3429, 2370, 1435. NMR (base libera, 300 MHz, $CDCl_3$, δ ppm): 8.19 (s br, 1H); 7.91-7.81 (m, 3H); 7.49 (dd, 2H); 7.39 (d, 2H); 7.29-7.12 (m, 4H); 7.01 (dd, 1H); 3.75 (s, 2H); 3.52 (tt, 1H); 3.12 (m, 2H); 2.63 (dq, 2H); 2.17 (dq, 2H); 1.53 (m, 2H). MS (m/z): 435 (MH^+).

I composti descritti nell' Esempio 2 ed Esempio 3 sono stati ottenuti seguendo la procedura descritta nell' Esempio 1.

Esempio 2

3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-1H-indolo cloridrato

M.p. = 189-190°C. NMR (base libera, 300 MHz, $CDCl_3$, δ ppm): 8.10 (s br, 1H); 7.77 (d,1H); 7.38 (d, 1H); 7.27-7.11 (m, 5H); 7.01 (dd, 1H); 3.80 (s, 2H); 3.53-3.40 (m, 1H); 3.13 (m, 2H); 2.67 (dq, 2H); 2.15 (dt, 2H); 1.64-1.49 (m, 2H). MS (m/z): 358 (M^+); 228; 194; 130.

Esempio 3

3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-2-metil-1H-indolo

M.p. = 168-170°C. IR (KBr, cm^{-1}) = 3401, 2904, 1432. NMR (300 MHz, $CDCl_3$, δ ppm): 7.80 (s br, 1H); 7.69 (m, 1H); 7.31-7.19 (m, 3H); 7.15-7.07 (m, 2H); 7.01 (dd, 1H); 3.73 (s, 2H); 3.45 (tt, 1H); 3.08 (m, 2H); 2.71-2.55 (m, 2H); 2.46 (s, 3H); 2.13 (m, 2H); 1.51 (m, 2H). MS (m/z): 372 (M^+); 230; 228; 144; 143.

Esempio 4

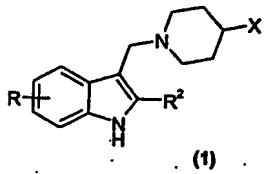
2-(4-Cloro-fenil)-3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-1H-indolo

Ad una soluzione di 48 mg (0.253 mmol) di 4-(2,6-dimetil-fenil)-piperidina in 1 mL di miscela MeOH:diossano (8:2 rispettivamente), si aggiungono a temperatura ambiente 0.021 mL (0.278 mmol) di CH_2O (37% soluzione acquosa) e 0.017 mL (0.304 mmol) di AcOH glaciale. Dopo agitazione per 20 minuti, si aggiunge una soluzione di 63 mg (0.326 mmol) di 2-(4-cloro-fenil)-1H-indolo in 2.5 mL di miscela MeOH:diossano (8:2 rispettivamente), e la miscela risultante viene agitata a temperatura ambiente durante la notte. La miscela di reazione viene versata su una cartuccia SCX ed eluita con 24 mL di CH_2Cl_2 e 36 mL di MeOH per rimuovere l'eccesso di materiale di partenza e quindi con 18 mL di una soluzione metanolica di ammoniaca al 3% per recuperare il composto finale. Il solvente viene rimosso *in vacuo*, ottenendo 100 mg di composto finale come solido bianco.

MS (m/z): 429 (MH^+).

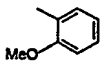
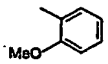
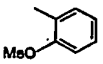
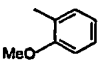
I composti di formula (1) e descritti in Tabella 1 sono stati ottenuti seguendo la procedura descritta nell'Esempio 4.

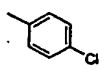
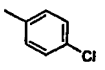
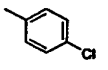
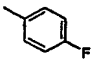
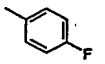
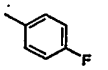
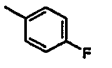
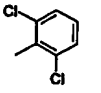
Tabella 1



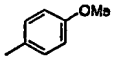
(1)

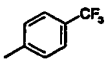
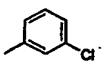
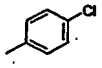
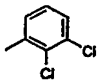
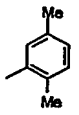
Es. no	R	R^2	X	MS (m/z)	Nome
5	H			435 (MH^+)	2-Fenil-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo
6	H			395 (MH^+)	3-[4-(2,6-Dimetil-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo
7	H			367 (MH^+)	2-Fenil-3-(4-fenil-piperidin-1-ilmetil)-1H-indolo
8	H			469 (MH^+)	2-(2-Cloro-fenil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1H-indolo
9	H			429 (MH^+)	2-(2-Cloro-fenil)-3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-1H-indolo
10	H			469 (MH^+)	2-(2-Cloro-fenil)-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo
11	H			401 (MH^+)	2-(2-Cloro-fenil)-3-(4-fenil-piperidin-1-

					ilmetil)-1H-indolo
12	H			465 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-2-(2-metossi-fenil)-1H-indolo
13	H			425 (MH^+)	3-[4-(2,6-Dimetil-fenil)-piperidin-1-ilmetil]-2-(2-metossi-fenil)-1H-indolo
14	H			46 (MH^+)	2-(2-Metossi-fenil)-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo
15	H			397 (MH^+)	2-(2-Metossi-fenil)-3-(4-fenil-piperidin-1-ilmetil)-1H-indolo
16	H			465 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-2-(3-metossi-fenil)-1H-indolo
17	H			425 (MH^+)	3-[4-(2,6-Dimetil-fenil)-piperidin-1-ilmetil]-2-(3-metossi-fenil)-1H-indolo
18	H			465 (MH^+)	2-(3-Metossi-fenil)-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo
19	H			397 (MH^+)	2-(3-Metossi-fenil)-3-(4-fenil-piperidin-1-

					ilmetil)-1H-indolo
20	H			469 (MH^+)	2-(4-Cloro-fenil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1H-indolo
21	H			469 (MH^+)	2-(4-Cloro-fenil)-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo
22	H			401 (MH^+)	2-(4-Cloro-fenil)-3-(4-fenil-piperidin-1-ilmetil)-1H-indolo
23	H			453 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-2-(4-fluoro-fenil)-1H-indolo
24	H			413 (MH^+)	3-[4-(2,6-Dimetil-fenil)-piperidin-1-ilmetil]-2-(4-fluoro-fenil)-1H-indolo
25	H			453 (MH^+)	2-(4-Fluoro-fenil)-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo
26	H			385 (MH^+)	2-(4-Fluoro-fenil)-3-(4-fenil-piperidin-1-ilmetil)-1H-indolo
27	H			425 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-2-furan-2-il-

					1H-indolo
28	H			385 (MH^+)	3-[4-(2,6-Dimetil-fenil)-piperidin-1-ilmetil]-2-furan-2-il-1H-indolo
29	H			425 (MH^+)	2-Furan-2-il-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo
30	H			357 (MH^+)	2-Furan-2-il-3-(4-fenil-piperidin-1-ilmetil)-1H-indolo
31	H			436 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-2-piridin-2-il-1H-indolo
32	H			396 (MH^+)	3-[4-(2,6-Dimetil-fenil)-piperidin-1-ilmetil]-2-piridin-2-il-1H-indolo
33	H			436 (MH^+)	2-Piridin-2-il-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo
34	H			368 (MH^+)	3-(4-Fenil-piperidin-1-ilmetil)-2-piridin-2-il-1H-indolo
35	H			441 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-2-tiofen-2-il-

					1H-indolo
36	H			401 (MH^+)	3-[4-(2,6-Dimetil-fenil)-piperidin-1-ilmetil]-2-tiofen-2-il-1H-indolo
37	H			441 (MH^+)	2-Tiofen-2-il-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo
38	H			373 (MH^+)	3-(4-Fenil-piperidin-1-ilmetil)-2-tiofen-2-il-1H-indolo
39	H			409 (MH^+)	2-Benzil-3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-1H-indolo
40	H			449 (MH^+)	2-Benzil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1H-indolo
41	H			397 (MH^+)	3-[4-(4-Metossi-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo
42	H			385 (MH^+)	3-[4-(2-Fluoro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo
43	H			385 (MH^+)	3-[4-(3-Fluoro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo

44	H			385 (MH^+)	3-[4-(4-Fluoro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo
45	H			435 (MH^+)	2-Fenil-3-[4-(4-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo
46	H			401 (MH^+)	3-[4-(2-Cloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo
47	H			401 (MH^+)	3-[4-(3-Cloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo
48	H			401 (MH^+)	3-[4-(4-Cloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo
49	H			381 (MH^+)	2-Fenil-3-(4-o-tolil-piperidin-1-ilmetil)-1H-indolo
50	H			445 (MH^+)	3-[4-(2-Bromo-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo
51	H			435 (MH^+)	3-[4-(2,3-Dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo
52	H			395 (MH^+)	3-[4-(2,5-Dimetil-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo

53	H			403 (MH^+)	3-[4-(2,6-Difluoro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo
54	H			445 (MH^+)	3-[4-(3-Bromo-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo
55	H			397 (MH^+)	3-[4-(2-Metossi-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo

Esempio 56

1-Benzil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo cloridrato

Sotto atmosfera di azoto, 13.2 mg (0.331 mmol) di NaH (60% dispersione in olio minerale) sono stati sospesi in 0.75 mL di DMF anidra. Dopo raffreddamento a 0°C, si aggiunge goccia a goccia una soluzione di 120 mg (0.276 mmol) di 3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo in 0.75 mL di DMF anidra. La miscela di reazione viene agitata 30 min, quindi 0.036 mL (0.304 mmol) di benzil bromuro vengono aggiunti goccia a goccia. La miscela di reazione viene lasciata riscaldare a temperatura ambiente ed agitata 2 h, quindi viene raffreddata a 0°C, si aggiunge acqua, seguita da NH_4OH conc. e la miscela risultante viene estratta con Et_2O. La fase organica viene anidrificata con Na_2SO_4 ed il solvente rimosso *in vacuo*, ottenendo 122 mg di prodotto grezzo, che viene quindi disciolto in CH_2Cl_2, la soluzione viene portata a pH acido con Et_2O/HCl ed il solvente viene rimosso *in*

vacuo. Il solido risultante viene triturato con acetone caldo, filtrato ed essiccato, ottenendo 53 mg del composto finale come solido bianco.

M.p. = 209-210 °C. NMR (base libera, 300 MHz, $CDCl_3$, δ ppm): 7.94 (m, 1H); 7.45-7.35 (m, 5H); 7.28-7.14 (m, 9H); 7.00 (dd, 1H); 6.95 (m, 1H); 5.23 (s, 2H); 3.68 (s, 2H); 3.43 (tt, 1H); 3.02 (m, 2H); 2.59 (dq, 2H); 2.04 (dt, 2H); 1.47 (m, 2H). MS (m/z): 525 (MH^+).

I composti descritti nell'esempio 57 e 58 sono stati ottenuti seguendo la procedura descritta nell'Esempio 56.

Esempio 57

3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1-propil-1H-indolo cloridrato

M.p. = 150-152°C. NMR (base libera, 300 MHz, $CDCl_3$, δ ppm): 7.91 (d, 1H); 7.51-7.39 (m, 5H); 7.36 (d, 1H); 7.27-7.19 (m, 3H); 7.15 (dd, 1H); 7.00 (t, 1H); 3.98 (dd, 2H); 3.63 (s, 2H); 3.41 (tt, 1H); 2.98 (m, 2H); 2.56 (dq, 2H); 2.00 (dt, 2H); 1.66 (m, 2H); 1.44 (m, 2H); 0.74 (t, 3H). MS (m/z): 476 ($M^{+\cdot}$); 248; 206; 178.

Esempio 58

3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-1-metil-2-fenil-1H-indolo cloridrato

M.p. = 179-184°C (dec.). NMR (base libera, 300 MHz, $CDCl_3$, δ ppm): 7.90 (d, 1H); 7.55-7.40 (m, 5H); 7.35 (d, 1H); 7.29-7.15 (m, 4H); 7.00 (t, 1H); 3.65 (s, 2H); 3.63 (s, 3H); 3.43 (tt, 1H); 3.01 (m, 2H); 2.58 (dq, 2H); 2.05 (dt, 2H); 1.46 (m, 2H). MS (m/z): 448 ($M^{+\cdot}$); 220; 204.

Esempio 59

3-(4-(2,6-Dicloro-fenil)piperidin-1-ilmetil)-1-(2-idrossietil)-2-fenil-1H-

Indolo cloridrato

Sotto atmosfera di azoto, 25 mg (0.62 mmol) di NaH (60% dispersione in olio minerale) vengono sospesi in 0.75 mL di DMF anidra. Dopo raffreddamento a 0°C, si aggiunge goccia a goccia una soluzione di 150 mg (0.344 mmol) di 3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo in 0.75 mL di DMF anidra. La miscela di reazione viene agitata 30 min, quindi 0.093 mL (0.62 mmol) di 2-(2-bromo-etossi)-tetraidro-pirano vengono aggiunti goccia a goccia. La miscela di reazione viene lasciata rinvenire a temperatura ambiente e agitata 2 h, quindi viene raffreddata a 0°C, si aggiunge acqua, seguita da NH_4OH conc., e la miscela risultante viene estratta con Et_2O. La fase organica viene anidrificata con Na_2SO_4 ed il solvente rimosso *in vacuo*, ottenendo 201 mg di grezzo, che viene discolto in una miscela di 2 mL di diossano e 3 mL di 1N HCl ed agitato 1 h a temperatura ambiente. Si aggiunge NH_4OH conc. fino a pH basico, quindi la miscela di reazione viene estratta con Et_2O, la fase organica viene anidrificata ed il solvente rimosso *in vacuo*, ottenendo 130 mg di composto grezzo che viene discolto in CH_2Cl_2, la soluzione viene portata a pH acido con Et_2O/HCl ed il solvente viene rimosso *in vacuo*. Il solido risultante viene cristallizzato da acetone, filtrato ed essiccato, ottenendo 44 mg del composto finale come solido bianco.

M.p. = 205-206 °C. NMR (base libera, 300 MHz, $CDCl_3$, δ ppm): 7.91 (d, 1H); 7.50-7.41 (m, 6H); 7.29-7.14 (m, 4H); 7.00 (dd, 1H); 4.21 (t, 2H); 3.79 (m, 2H); 3.62 (s, 2H); 3.41 (tt, 1H); 2.98 (m, 2H); 2.56 (dq, 2H); 2.01 (dt, 2H); 1.45 (m, 3H). MS (m/z): 478 ($M^{+\cdot}$); 250.

Esempio 60

1-(4-*tert*-Butil-benzil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo trifluoroacetato

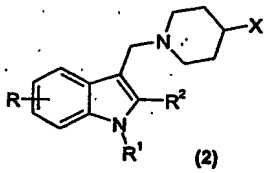
Ad una soluzione di 70 mg (0.16mmol) di 3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo in 0.5 mL di DMF anidra, si aggiungono 15mg (0.37 mmol) di NaH (60% dispersione in olio minerale). Dopo agitazione per 15 min a temperatura ambiente sotto atmosfera di argo, si aggiungono 0.1 mL di una soluzione 2M di 4-*tert*-butil-benzilbromuro in DMF; dopo agitazione per 75 min si effettua una seconda aggiunta di 0.1 mL di una soluzione 2M di 4-*tert*-butil-benzilbromuro in DMF e la miscela risultante viene agitata a temperatura ambiente durante la notte. La reazione viene arrestata con poche gocce di acqua, versata su una cartuccia Chem-elute per trattenere l'acqua ed eluita con AcOEt; la soluzione risultante viene concentrata e quindi versata su una cartuccia SCX ed eluita con MeOH per eliminare impurezze non-basiche e quindi con una soluzione metanolica al 3% di ammoniaca per recuperare il composto finale. Il solvente viene rimosso *in vacuo* e il grezzo risultante viene purificato per HPLC preparativa su una colonna Symmetry C18, per gradiente di eluizione, con un sistema solvente acqua/TFA 99.9:0.1 rispettivamente (A) e CH_3CN/TFA 99.9:0.1 rispettivamente (B) con il seguente gradiente: 25% B (1min); 25% B→95% B (8min); 95% B→25% B (1min), ottenendo 27 mg di composto finale.

MS (m/z): 581 (MH^+).

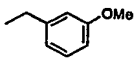
I composti di formula (2) descritti nella Tabella 2 sono stati ottenuti

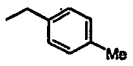
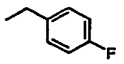
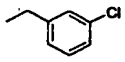
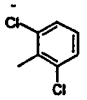
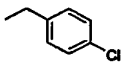
seguendo la procedura descritta nell'esempio 60.

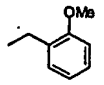
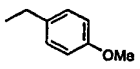
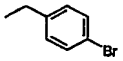
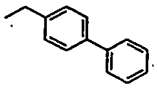
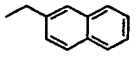
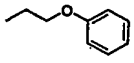
Tabella 2

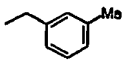
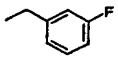
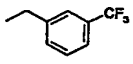
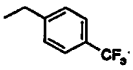


(2)

Es. no	R	R^1	R^2	X	MS (m/z)	Nome
61	H	$CH_2CH_2CHMe_2$			505 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-1-(3-metil-butil)-2-fenil-1H-indolo
62	H	Ciclopropilmetil			489 (MH^+)	1-Ciclopropilmetil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo
63	H				555 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-1-(3-metossi-benzil)-2-fenil-1H-indolo
64	H				539 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-1-(2-metil-benzil)-2-fenil-1H-indolo
65	H				531 (MH^+)	1-Cicloesilmetil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo

66	H				539 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-1-(4-metil-benzil)-2-fenil-1H-indolo
67	H				543 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-1-(4-fluoro-benzil)-2-fenil-1H-indolo
68	H				559 (MH^+)	1-(3-Cloro-benzil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo trifluoroacetato
69	H				559 (MH^+)	1-(2-Cloro-benzil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo
70	H				559 (MH^+)	1-(4-Cloro-benzil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo
71	H	Allil			475 (MH^+)	1-Allil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo
72	H	Propargil			473 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1-prop-2-inil-1H-indolo

73	H				555 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-1-(2-metossi-benzil)-2-fenil-1H-indolo trifluoroacetato
74	H				555 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-1-(4-metossi-benzil)-2-fenil-1H-indolo trifluoroacetato
75	H				603 (MH^+)	1-(4-Bromo-benzil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo trifluoroacetato
76	H				601 (MH^+)	1-Bifenil-4-ilmetil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo trifluoroacetato
77	H				575 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-1-naftalen-2-ilmetil-2-fenil-1H-indolo trifluoroacetato
78	H				555 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-1-(2-fenossi-etil)-2-fenil-1H-indolo trifluoroacetato

79	H				539 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-1-(3-metil-benzil)-2-fenil-1H-indolo trifluoroacetato
80	H				543 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-1-(2-fluoro-benzil)-2-fenil-1H-indolo trifluoroacetato
81	H				543 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-1-(3-fluoro-benzil)-2-fenil-1H-indolo trifluoroacetato
82	H				593 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1-(2-trifluorometil-benzil)-1H-indolo trifluoroacetato
83	H				593 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1-(3-trifluorometil-benzil)-1H-indolo trifluoroacetato
84	H				593 (MH^+)	3-[4-(2,6-Dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1-(4-trifluorometil-benzil)-1H-indolo

						trifluoroacetato

Esempio 85

1-Benzensolfonil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo trifluoroacetato

100 mg (0.229 mmol) di 3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo vengono discolti in 3 mL di un sistema bifasico consistente di una miscela 1:1 di toluene e NaOH acquosa al 50%; due gocce di Aliquat® 336 vengono aggiunte e il sistema viene agitato vigorosamente per 15 min, quindi vengono aggiunti 0.037 mL di benzensolfonil cloruro; due ulteriori aggiunte di 0.015 mL di cloruro vengono effettuate durante un periodo di 20 h di agitazione a temperatura ambiente. La miscela risultante viene versata su una cartuccia Chem-elute per eliminare l'acqua ed eluita con etil acetato; il filtrato viene evaporato *in vacuo* e il residuo viene purificato per HPLC preparativa su una colonna Symmetry C18, attraverso gradiente di eluizione con un sistema solvente acqua/TFA 99.9:0.1 rispettivamente (A) e CH_3CN/TFA 99.9:0.1 rispettivamente (B) con il seguente gradiente: 25% B (1min); 25% B→95% B (8min); 95% B→25% B (1min), ottenendo 29 mg del composto finale.

MS (m/z): 575 (MH^+).

Il composto descritto nell'Esempio 86 è stato ottenuto seguendo la procedura descritta nell' Esempio 85.

Esempio 86

1-Benzoil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo

trifluoroacetato

MS (m/z): 539 (MH^+).

Test farmacologici

Studi di legame recettoriale

Gli studi di legame recettoriale sono stati effettuati su piastre da 96 pozzetti; il medium di incubazione è costituito da Tris HCl pH 7.4 (4°C) contenente 100 μg/mL di bacitracina, 4 μg/mL di leupeptina e 2 μg/mL di chimostatina con un volume finale di 0.75 mL, utilizzando come radiolegante [^{3}H]-nociceptina (Amersham, 172 Ci/mmol). I campioni sono stati incubati a 25°C per 20 min. e quindi sono stati filtrati tramite filtri Whatman GF/B pretrattati con 0.2% polietilenimmina. I filtri sono stati lavati 2 volte con tampone Tris HCl pH 7.4 (4°C). La radioattività presente sui filtri è stata misurata utilizzando un contatore beta 2500 Canberra Packard.

I più potenti composti di formula (I) secondo la presente invenzione hanno una affinità di legame (Ki) ai recettori ORL-1 nell'intervallo tra 0.1 e 1000 nM.

Preparazione di membrana per il test di binding GTPγS

L'intera procedura è stata effettuata a 4°C. Il tampone utilizzato è costituito da Tris HCl 10 mM, EDTA 0.1 mM, pH 7.4 (4°C) (T.E.).

Le cellule rimosse dalle flask di coltura vengono centrifugate a bassa velocità per rimuovere il medium di crescita.

1. Risospendere i pellets (una flask T175cm^2 in 0.5-1 mL T.E.).
2. Omogeneizzare le cellule utilizzando un Ultra-Turrax.
3. Centrifugare l'omogenato a 1500 rpm per 10 min a 4°C.

4. Scartare i pellets P1.
5. Centifugare il surnatante a 14000 rpm per 30 min.
6. Scartare il surnatante.
7. Risospendere i pellets P2 per aspirazione (frazione microsomiale) in 200 mL di T.E. e conservare congelati a –80°C.

Per la stima delle proteine, diluire la preparazione 3 x in T.E. e saggiare contro curva standard BSA 0-2 mg/mL in T.E.. La concentrazione proteica è normalmente compresa tra 1 e 4 mg/mL. La resa tipica è 1 mg di proteine per flask T175cm^2 a confluenza.

Test di binding [^{35}S]-GTPγS

I test sono stati effettuati in formato 96 pozzetti utilizzando il metodo modificato da Wieland e Jacobs (*Methods Enzymol.*, 1994, **237**, 3-13). Le membrane (10 µg per pozzetto) ed i granuli SPA di agglutinina di germe di grano (Amersham Pharmacia) (0.5 mg per pozzetto) sono stati premiscelati in tampone (HEPES 20 mM, NaCl 100 mM, $MgCl_2$ 10 mM, pH 7.4, 4°C) e preincubati con 10 µM GDP. Concentrazioni crescenti dei composti da testare sono state quindi incubate con la miscela membrana/granuli per 30 min a temperatura ambiente. Sono stati poi aggiunti 0.3 nM [^{35}S]-GTPγS (1170 Ci/mmol, Amersham) e 30 µM nociceptina. Il volume totale del saggio è 100 µL per pozzetto. Le piastre vengono quindi incubate a temperatura ambiente per 30 min sotto agitazione e quindi centrifugate a 1500 g per 5 min. La quantità di [^{35}S]-GTPγS legato alle membrane è stata determinata mediante un contatore di scintillazione Wallac 1450 microbeta Trilux.

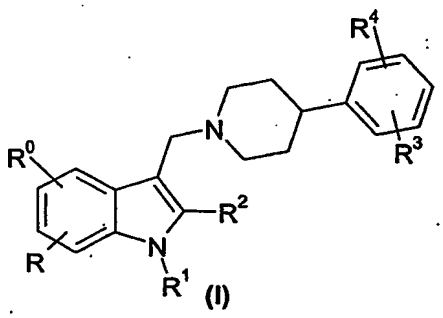
L'attività del composto viene valutata come inibizione della stimolazione

del binding di [^{35}S]-GTPγS indotta dall'agonista (nociceptina).

I valori di pIC50 vengono determinati come la concentrazione del composto che causa una inibizione del 50% della risposta della nociceptina.

RIVENDICAZIONI

1. Composto di formula (I)



(I)

dove:

R e **R^0** sono ciascuno indipendentemente idrogeno, alogeno, C_{1-6}alchile, peraloC_{1-6}alchile, C_{1-6}alcossi, idrossi, ammino, C_{1-6}alchilammino, di(C_{1-6}alchil)ammino, amminoC_{1-6}alchile, (C_{1-6}alchil)amminoC_{1-6}alchile, di(C_{1-6}alchil)amminoC_{1-6}alchile, arile.

R^1 è idrogeno, C_{1-6}alchile, C_{3-6}alchenil, C_{3-6}alchinil, arilC_{1-6}alchile, eteroarilC_{1-6}alchile, (C_{3-7}cicloalchil)alchile, amminoC_{1-6}alchile, (C_{1-6}alchil)amminoC_{1-6}alchile, di(C_{1-6}alchil)amminoC_{1-6}alchile, idrossiC_{1-6}alchile, C_{1-6}alcossiC_{1-6}alchile, arilossiC_{1-6}alchile, COarile, SO_2arile dove ciascun arile o eteroarile può essere sostituito una o più volte da alogeno, C_{1-6}alcossi, C_{1-6}alchile, idrossi, ammino, C_{1-6}alchilammino, di(C_{1-6}alchil)ammino, amminoC_{1-6}alchile, (C_{1-6}alchil)amminoC_{1-6}alchile, di(C_{1-6}alchil)amminoC_{1-6}alchile, arile o peraloC_{1-6}alchile.

R^2 è C_{3-7}cicloalchile, arile, eteroarile, arilC_{1-6}alchile, eteroarilC_{1-6}alchile, dove ciascun arile o eteroarile può essere sostituito una o più volte da alogeno, C_{1-6}alcossi, C_{1-6}alchile, idrossi, ammino, C_{1-6}alchilammino, di(C_{1-6}alchil)ammino, amminoC_{1-6}alchile, (C_{1-6}alchil)amminoC_{1-6}alchile, di(C_{1-6}alchil)amminoC_{1-6}alchile, arile o peraloC_{1-6}alchile.

$_6$alchil)amminoC$_{1-6}$alchile, di(C$_{1-6}$alchil)amminoC$_{1-6}$alchile, arile o peraloC$_{1-6}$alchile.

R^3 e R^4 sono ciascuno indipendentemente idrogeno, alogeno, C$_{1-6}$alchile, peraloC$_{1-6}$alchile, C$_{1-6}$alcossi, idrossi, ammino, C$_{1-6}$alchilammino, di(C$_{1-6}$alchil)ammino, amminoC$_{1-6}$alchile, (C$_{1-6}$alchil)amminoC$_{1-6}$alchile, di(C$_{1-6}$alchil)amminoC$_{1-6}$alchile, arile.

2. Composto secondo la rivendicazione 1, dove R ed R^0 sono idrogeno, cloro, fluoro, metile, metossi.
3. Composto secondo le rivendicazioni 1-2, dove R^1 è idrogeno, metile, n-propile, isopentile, allile, 2-idrossietile, ciclopropilmetile, cicloesilmetile, benzile, fluorobenzile, clorobenzile, bromobenzile, metossibenzile, metilbenzile, *t*-butilbenzile, trifluorometilbenzile, bifenilmetile, fenossietile, 2-naftilmetil, benzoile, benzensolfonile.
4. Composto secondo le rivendicazioni 1-3, dove R^2 è fenile, clorofenile, metossifenile, fluorofenile, 2-furile, 2-thienile, 2-piridile, benzile.
5. Composto secondo le rivendicazioni 1-4, dove R^3 e R^4 sono idrogeno, cloro, fluoro, bromo, metile, metossi, trifluorometile.
6. Composto secondo la rivendicazione 1, scelto tra:

   3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

   3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1H-indolo;

   3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-metil-1H-indolo;

   2-(4-cloro-fenil)-3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-1H-indolo;

   2-fenil-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

   3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

   2-fenil-3-(4-fenil-piperidin-1-ilmetil)-1H-indolo;

2-(2-cloro-fenil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-(2-cloro-fenil)-3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-(2-cloro-fenil)-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-(2-cloro-fenil)-3-(4-fenil-piperidin-1-ilmetil)-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-(2-metossi-fenil)-1H-indolo;

3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-2-(2-metossi-fenil)-1H-indolo;

2-(2-metossi-fenil)-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-(2-metossi-fenil)-3-(4-fenil-piperidin-1-ilmetil)-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-(3-metossi-fenil)-1H-indolo;

3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-2-(3-metossi-fenil)-1H-indolo;

2-(3-metossi-fenil)-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-(3-metossi-fenil)-3-(4-fenil-piperidin-1-ilmetil)-1H-indolo;

2-(4-cloro-fenil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-(4-cloro-fenil)-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-(4-cloro-fenil)-3-(4-fenil-piperidin-1-ilmetil)-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-(4-fluoro-fenil)-1H-indolo;

3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-2-(4-fluoro-fenil)-1H-indolo;

2-(4-fluoro-fenil)-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-(4-fluoro-fenil)-3-(4-fenil-piperidin-1-ilmetil)-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-furan-2-il-1H-indolo;

3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-2-furan-2-il-1H-indolo;

2-furan-2-il-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-furan-2-il-3-(4-fenil-piperidin-1-ilmetil)-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-piridin-2-il-1H-indolo;

3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-2-piridin-2-il-1H-indolo;

2-piridin-2-il-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

3-(4-fenil-piperidin-1-ilmetil)-2-piridin-2-il-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-tiofen-2-il-1H-indolo;

3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-2-tiofen-2-il-1H-indolo;

2-tiofen-2-il-3-[4-(2-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

3-(4-fenil-piperidin-1-ilmetil)-2-tiofen-2-il-1H-indolo;

2-benzil-3-[4-(2,6-dimetil-fenil)-piperidin-1-ilmetil]-1H-indolo;

2-benzil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1H-indolo;

3-[4-(4-metossi-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2-fluoro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(3-fluoro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(4-fluoro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

2-fenil-3-[4-(4-trifluorometil-fenil)-piperidin-1-ilmetil]-1H-indolo;

3-[4-(2-cloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(3-cloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(4-cloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

2-fenil-3-(4-o-tolil-piperidin-1-ilmetil)-1H-indolo;

3-[4-(2,3-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2-bromo-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2,5-dimetil-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2,6-difluoro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(3-bromo-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2-metossi-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

1-benzil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1-propil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-metil-2-fenil-1H-indolo;

3-(4-(2,6-dicloro-fenil)piperidin-1-ilmetil)-1-(2-idrossietil)-2-fenil-1H-indolo;

1-(4-*tert*-butil-benzil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(3-metil-butil)-2-fenil-1H-indolo;

1-ciclopropilmetil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(3-metossi-benzil)-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(2-metil-benzil)-2-fenil-1H-indolo;

1-cicloesilmetil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(4-metil-benzil)-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(4-fluoro-benzil)-2-fenil-1H-indolo;

1-(3-cloro-benzil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

1-(2-cloro-benzil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

1-(4-Cloro-benzil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

1-allil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1-prop-2-inil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(2-metossi-benzil)-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(4-metossi-benzil)-2-fenil-1H-indolo;

1-(4-bromo-benzil)-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

1-bifenil-4-ilmetil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-naftalen-2-ilmetil-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(2-fenossi-etil)-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(3-metil-benzil)-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(2-fluoro-benzil)-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-1-(3-fluoro-benzil)-2-fenil-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1-(2-trifluorometil-benzil)-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1-(3-trifluorometil-benzil)-1H-indolo;

3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1-(4-trifluorometil-benzil)-1H-indolo;

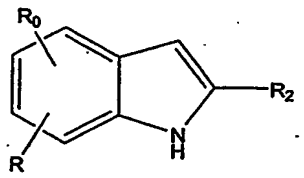
1-benzensolfonil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo;

1-benzoil-3-[4-(2,6-dicloro-fenil)-piperidin-1-ilmetil]-2-fenil-1H-indolo.

7. Enantiomero di un composto di formula (I) come descritta nella rivendicazione 1.
8. Miscela di enantiomeri di un composto di formula (I) come descritta nella rivendicazione 1, dove un enantiomero è presente in proporzione maggiore rispetto al suo antipodo.
9. Composto di formula (I) come definito nella rivendicazione 1, per uso come sostanza terapeutica attiva.
10. Composizione farmaceutica comprendente un composto di formula (I) come definito nella rivendicazione 1, o un suo sale o idrato

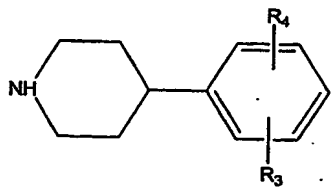
farmaceuticamente accettabile, associato ad uno o più eccipienti farmaceuticamente accettabili.

11. Processo per la preparazione di un composto di formula (I) come definito nella rivendicazione 1, dove R1 è idrogeno, comprendente il trattamento di un composto di formula (II)



(II)

in cui R, R0 ed R2 hanno i significati indicati nella rivendicazione 1, con formaldeide ed un composto di formula (III)



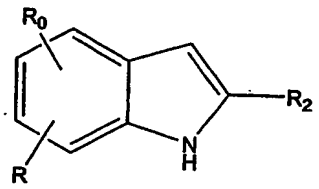
(III)

dove R3 ed R4 hanno i significati indicati nella rivendicazione 1, ottenendo così i composti di formula (I) in cui R1 è idrogeno.

12. Processo secondo la rivendicazione 11, dove la reazione di conversione del composto (II) in composto (I) è una reazione di Mannich.

13. Processo secondo la rivendicazione 12, dove la reazione di Mannich si svolge in ambiente di solvente organico, in presenza di formaldeide ed acido acetico.

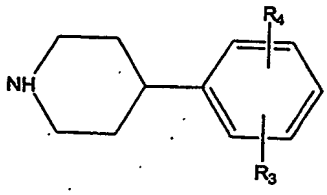
14. Processo per la preparazione di un composto di formula (I) come definito nella rivendicazione 1, dove R1 è diverso da idrogeno, comprendente il trattamento di un composto di formula (II)



(II)

in cui R, R0 ed R2 hanno i significati indicati nella rivendicazione 1, secondo i due passaggi seguenti, che possono aver luogo in qualsiasi ordine:

(a): trattamento con formaldeide ed un composto di formula (III)



(III)

dove R3 ed R4 sono come definiti nella rivendicazione 1,

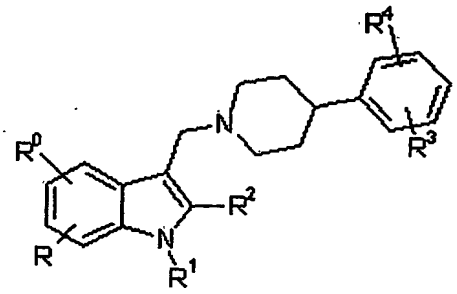
(b) trattamento con un composto di formula R1-X, in cui R1 è come definito nella rivendicazione 1 ed X è un adatto gruppo uscente, ottenendo così i composti di formula (I), in cui R1 è diverso da idrogeno.

15. Processo secondo la rivendicazione 14, dove il passaggio (a) avviene attraverso una reazione di Mannich.

16. Processo secondo la rivendicazione 15, dove detta reazione di Mannich si svolge in ambiente di solvente organico, in presenza di formaldeide ed acido acetico.

17. Processo secondo le rivendicazioni 14-16, dove il passaggio (b) avviene in presenza di una base forte, oppure in condizioni di trasferimento di fase.

18. Uso di un composto di formula (IA)



(IA)

dove:

R e **R⁰** sono ciascuno indipendentemente idrogeno, alogeno, C_{1-6}alchile, peraloC_{1-6}alchile, C_{1-6}alcossi, idrossi, ammino, C_{1-6}alchilammino, di(C_{1-6}alchil)ammino, amminoC_{1-6}alchile, (C_{1-6}alchil)amminoC_{1-6}alchile, di(C_{1-6}alchil)amminoC_{1-6}alchile, arile.

R¹ è idrogeno, C_{1-6}alchile, C_{3-6}alchenil, C_{3-6}alchinil, arilC_{1-6}alchile, eteroarilC_{1-6}alchile, (C_{3-7}cicloalchil)alchile, amminoC_{1-6}alchile, (C_{1-6}alchil)amminoC_{1-6}alchile, di(C_{1-6}alchil)amminoC_{1-6}alchile, idrossiC_{1-6}alchile, C_{1-6}alcossiC_{1-6}alchile, arilossiC_{1-6}alchile, COarile, SO_2arile dove ciascun arile o eteroarile può essere sostituito una o più volte da alogeno, C_{1-6}alcossi, C_{1-6}alchile, idrossi, ammino, C_{1-}

$_6$alchilammino, di(C_{1-6}alchil)ammino, amminoC$_{1-6}$alchile, (C_{1-6}alchil)amminoC$_{1-6}$alchile, di(C_{1-6}alchil)amminoC$_{1-6}$alchile, arile o peraloC$_{1-6}$alchile.

R² è idrogeno, C_{1-6}alchile, C_{3-7}cicloalchile, arile, eteroarile, arilC$_{1-6}$alchile, eteroarilC$_{1-6}$alchile, dove ciascun arile o eteroarile può essere sostituito una o più volte da alogeno, C_{1-6}alcossi, C_{1-6}alchile, idrossi, ammino, C_{1-6}alchilammino, di(C_{1-6}alchil)ammino, amminoC$_{1-6}$alchile, (C_{1-6}alchil)amminoC$_{1-6}$alchile, di(C_{1-6}alchil)amminoC$_{1-6}$alchile, arile o peraloC$_{1-6}$alchile.

R³ e **R⁴** sono ciascuno indipendentemente idrogeno, alogeno, C_{1-6}alchile, peraloC$_{1-6}$alchile, C_{1-6}alcossi, idrossi, ammino, C_{1-6}alchilammino, di(C_{1-6}alchil)ammino, amminoC$_{1-6}$alchile, (C_{1-6}alchil)amminoC$_{1-6}$alchile, di(C_{1-6}alchil)amminoC$_{1-6}$alchile, arile,

nella preparazione di un farmaco per somministrazione ad un paziente umano o animale per modulare l'attività dei recettori ORL-1.

19. Uso secondo la rivendicazione 18, dove detto farmaco è utile nella profilassi e trattamento di malattie dipendenti dalla modulazione del recettore ORL-1.

20. Uso secondo le rivendicazioni 18-19, dove dette malattie sono scelte tra dolore acuto, dolore cronico neuropatico o infiammatorio, includendo la neuralgia postherpetica, neuralgia, neuropatia diabetica, dolore post-infartuale, dolore viscerale incluso quello associato alla sindrome da colon irritabile, dismenorrea, iperriflessia della vescica, osteoartrite, dolore alla schiena, travaglio doloroso in gravidanza, terapia della tolleranza e dipendenza da oppioidi,

disordini alimentari quali l'anoressia e bulimia, ansietà e condizioni di stress, disordini gastrointestinali inclusa la sindrome da colon irritabile e sintomi associati con dispepsia non ulcerosa e riflusso gastroesofageo, malattie del sistema immunitario, disfunzioni del sistema cardiovascolare, perdita di memoria, disordini cognitivi, danni motori e neurodegenerazione dovuta a malattia di Alzheimer, demenza senile, malattia di Parkinson o altre patologie neurodegenerative, infarto, epilessia, diuresi alterata e escrezione di sodio, sindrome di inappropriata secrezione di ormone antidiuretico (SIADH), sindrome adulta da stress respiratorio (ARDS), insufficienza cardiaca congestizia, cirrosi con asciti, disfunzioni sessuali tra cui l'impotenza e la frigidità, alterata funzione polmonare, includendo la malattia cronica da ostruzione polmonare, tosse, asma, depressione, abuso di droghe tra cui abuso di alcol, demenze quali demenza vascolare e demenza associata ad AIDS, disordini metabolici tra cui l'obesità, omeostasi idrica ed escrezione di sodio e patologie associate alle alterazioni della pressione arteriosa.

(GER/pd)

Milano, lì 4 Luglio 2003

p. GLAXOSMITHKLINE S.p.A.

Il Mandatario

Dr.ssa Gemma Gervasi

NOTARBARTOLO & GERVASI S.p.A.

CAMERA DI COMMERCIO IND. ART. E AGRICOLTURA - MILANO -

SEAL

MINISTRY OF PRODUCTIVE ACTIVITIES
GENERAL DIRECTORATE FOR PRODUCTION DEVELOPMENT AND COMPETITIVITY
Italian Patent and Trademark Office
OFFICE G2

****

Authentication of copy of documents concerning the Patent application for INDUSTRIAL INVENTION No. MI2003A001378

It is hereby certified that the attached copy is the true copy of the original documents filed with the above mentioned patent application whose data are shown in the enclosed filing certificate.

Rome, May 18, 2004

Director of the Division
(signature)
Dr. Paola Giuliano

SEAL

FORM A
DUTY STAMP

TO THE MINISTRY OF INDUSTRY COMMERCE AND HANDICRAFT
Italian Patent and Trademark Office - ROME
Patent Application for Industrial Invention, filing of reserves, advanced opening to public inspection

A. Applicant
1) Name GLAXOSMITHKLINE S.P.A. (Joint Stock Company)
Residence VERONA code 00212840235
2) Name
Residence code

B. APPLICANT'S REPRESENTATIVE BEFORE IPTO
Surname, name Dr. Gemma Gervasi et al Fiscal code
Name of the corresp. office NOTARBARTOLO & GERVASI S.p.A.
Address Corso di Porta Vittoria 9 City Milan code 20122 prov MI

C. ELECTED DOMICILE OF THE ADDRESSEE
Address No. city code
prov

D. TITLE proposed class, (sec./cl./ucl.) C07D group/subgroup

NEW 3-SUBSTITUTED INDOLE LIGANDS FOR THE ORL-1 RECEPTOR

ADVANCED OPENING TO PUBLIC INSPECTION yes___ no _X
in presence of amendment request: date no. of ref.:

E. NAMED INVENTORS
surname, name
1) FARINA Carlo
2) RONZONI Silvano
surname, name
3) VALLESE Stefania
4) CONSONNI Alessandra

F. PRIORITY
Country or Exhibition Type of Priority Appln. No. Appln. date Encl(yes/res)
1) NONE
2)

G. CENTRE FOR COLLECTING MICROORGANISMS'CULTURES, denomination

H. SPECIAL NOTES
NONE

ENCLOSED DOCUMENTS No. Doc.		RESERVES DISSOLUTION	
Doc.1) 1 prov. no. sheets 56	abstract with main drawing, spec. and claims (compulsory 1 copy)	Date	Filing. No.
Doc.2) 0 prov. No. Draw. 00	drawings (compulsory if cited in the description, 1 copy)		
Doc.3) 1 res.	power of attorney or reference to general power of attorney		
Doc.4) 0 res.	designation of inventor		
Doc.5) 0 res.	priority doc. with Italian transl	Comparison single prio.	
Doc.6) 0 res.	authorisation or assignment deed		
Doc.7) 0 res.	complete name of the applicant		

8) PAYMENT RECEIPT OF EUR 291,80 + 180,76 compulsory

filled in on 04.07.2003 The applicant's signature Gemma Gervasi follows yes/no NO
We require a certified copy of the present deed yes/no YES

PROVINCIAL OFFICE OF INDUSTRY COMMERCE HANDICRAFT OF MILAN code 15

FILING CERTIFICATE Application no. MI2003A001378 Reg. A

The year 2003, the day 04 of the month of July

The above mentioned applicant(s) has(have) presented to me undersigned the present application consisting of no. 00 additional sheets for the grant of the above patent.

I. NOTES OF THE RECORDING OFFICER

THE DEPOSITER
(signature)

THE RECORDING OFFICER
(signature)
M. Cortonesi

FORM A

ABSTRACT OF THE INVENTION TOGETHER WITH MAIN DRAWING, DESCRIPTION AND CLAIM

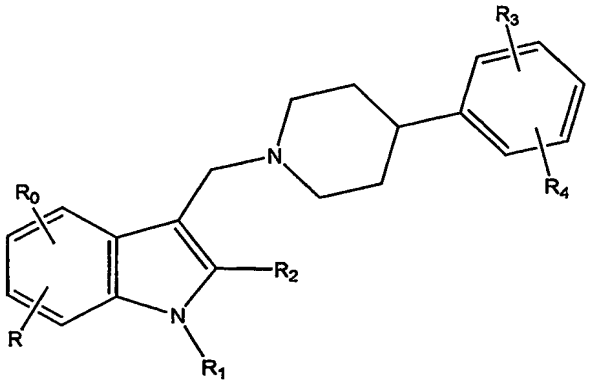
Application No. MI2003A001378 Reg.A Filing date 04.07.2003
Patent No. Date of grant

D. TITLE

NEW 3-SUBSTITUTED INDOLE LIGANDS FOR THE ORL-1 RECEPTOR

L. ABSTRACT

New ligands for the ORL-1 receptor are described, useful for modulating the activity of said receptors in a patient in need thereof, and for preventing and treating illnesses dependent on the stimulation of this receptor. The new compounds conform to structural formula (I)



(I)

M. DRAWING

Description of the Patent Application for the industrial invention entitled:

NEW 3-SUBSTITUTED INDOLE LIGANDS FOR THE ORL-1 RECEPTOR

Applicant: GLAXOSMITHKLINE S.P.A.

Residing in VERONA

named inventors: FARINA Carlo,VALLESE Stefania, RONZONI Silvano, CONSONNI Alessandra

filed on 04.07.2003 under No. MI2003A001378

* * * * *

The present invention relates to certain new compounds, a process for their preparation, to pharmaceutical compositions which contain them, and to the use of these compounds in medicine. The invention relates in particular to a group of new compounds possessing antagonistic or agonistic activity for the receptors ORL-1 and useful in treating illness related to modulation of these receptors.

The ORL-1 receptor is located along the entire neural axis and is involved in various pathological phenomena, including the transmission of pain. Various peptide and non-peptide ligands for the ORL-1 receptor are known; the non-peptide ligands include known compounds with morphinan, benzimidazopiperidine, spiropiperidine, arylpiperidine and 4-aminoquinoline structure (Life Sciences, 73, 2003, 663-678): WO 0183454 and WO 03040099 describe other ORL-1 antagonists with benzosuberonylpiperidine structure substituted in position 5 by a hydroxy, alkoxy, amino or alkylamino group, and their synthesis method.

J.Med.Chem., 1997, 40(23), 3912-14 and WO 9709308 describe certain indoles substituted in position 3 with a dipiperazine group, as antagonists for the receptor NPY-1.

J.Med.Chem., 1996, 39(10), 1941-2, WO 9424105, WO 9410145, WO 02241894, WO 9629330 and GB 2076810 describe variously substituted 3-piperazinylmethyl indoles as ligands for dopamine receptors, in particular for the D4 receptor.

GB 2083476 describes specific 3-arylpiperidinylmethyl indoles as 5HT uptake inhibitors.

US 5215989 describes certain di-substituted piperazine and imidazole derivatives

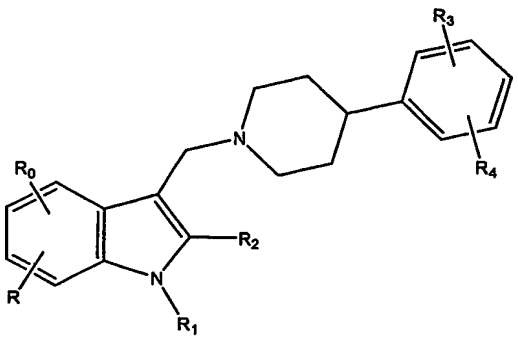
useful as class III antiarrhythmic agents.

EP 846683 describes hydroxypiperidine derivatives as NMDA receptor blockers.

It has now been found that certain 3-aminomethylindoles are powerful ligands for the ORL-1 receptor, and can therefore be useful as analgesics in man or animals in treating, for example, acute pain; chronic neuropathic or inflammatory pain, including post-herpes neuralgia, neuralgia, diabetic neuropathy and post-infarct pain; visceral pain including that associated with irritable bowel syndrome, dysmenorrhea, and hyperreflexia of the bladder; osteoarthritis, back pain, labour pain in childbirth and therapy of opioid tolerance and dependence.

These compounds can therefore be useful in the treatment or prophylaxis of eating disorders such as anorexia and bulimia; anxiety and stress condition; gastrointestinal disorders including irritable bowel syndrome, and symptoms associated with non-ulcerous dyspepsia and gastro-oesophageal reflux; diseases of the immune system; dysfunctions of the cardiovascular system; loss of memory, cognitive disorders, motor damage and neurodegeneration due to Alzheimer's disease; senile dementia, Parkinson's disease or other neurodegenerative pathologies; infarct; epilepsy; altered diuresis and sodium excretion; syndrome of inappropriate anti-diuretic hormone secretion (SIADH); adult respiratory distress syndrome (ARDS); congestive cardiac insufficiency; cirrhosis with ascites; sexual dysfunctions including impotence and frigidity; and altered pulmonary function, including chronic obstructive pulmonary disease. These compounds can also be useful in the treatment or prophylaxis of cough; asthma; depression; drug abuse such as alcohol abuse; dementia such as vascular dementia and dementia associated with AIDS; metabolic disorders such as obesity; pathologies associated with alterations of arterial pressure, and for water homeostasis and sodium excretion.

The compounds of the invention conform to structural formula (I)



(I)

wherein:

R and R^0 are each independently hydrogen, halogen, C_{1-6}alkyl, perhaloC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aryl.

R^1 is hydrogen, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkinyl, arylC_{1-6}alkyl, heteroarylC_{1-6}alkyl, (C_{3-7}cycloalkyl)alkyl, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, aryloxyC_{1-6}alkyl, CO-aryl, SO_2aryl where each aryl or heteroaryl can be substituted one or more times by halogen, C_{1-6}alkoxy, C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aryl or perhaloC_{1-6}alkyl.

R^2 is C_{3-7}cycloalkyl, aryl, heteroaryl, arylC_{1-6}alkyl, heteroarylC_{1-6}alkyl, where each aryl or heteroaryl can be substituted one or more times by halogen, C_{1-6}alkoxy, C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aryl or perhaloC_{1-6}alkyl.

R^3 and R^4 are each independently hydrogen, halogen, C_{1-6}alkyl, perhaloC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aryl.

The compounds of formula (I) can exhibit stereoisomerism because of the presence of chiral atoms and/or multiple bonds. The present invention therefore extends to stereoisomers of the compounds of the formula (I), including racemes,

enantiomers, diastereoisomers and geometric isomers.

It has been found that, when a compound of formula (I) exhibits optical isomerism, an enantiomer possesses a greater affinity for the ORL-1 receptor than its antipod.

Consequently, the present invention also provides an enantiomer of a compound of formula (I).

In a further aspect, the present invention provides a mixture of enantiomers of a compound of formula (I) where an enantiomer is present in a proportion greater than its antipod.

As aforestated, the compounds of formula (I) are ligands for the ORL-1 receptor. Hence, a compound of formula (I) is provided as active therapeutic substance.

According to another aspect of the present invention a method is provided for modulating the activity of the ORL-1 receptor in a human or animal patient in need thereof, comprising administering to the human or animal patient an effective quantity of a compound of formula (I).

Another aspect of the present invention provides the use of a compound of formula (I) in preparing a medicament for human or animal administration, useful for modulating the activity of the ORL-1 receptor.

Said compounds of formula 1 can be agonists or antagonists of the ORL-1 receptor.

According to a particular aspect of the present invention, an antagonist of formula (I) can be used as an analgesic in human or animal patients for the treatment, for example, of acute pain; chronic neuropathic or inflammatory pain, including post-herpes neuralgia, neuralgia, diabetic neuropathy and post-infarct pain; visceral pain including that associated with irritable bowel syndrome, dysmenorrhea, and hyperreflexia of the bladder; osteoarthritis, back pain, labour pain in childbirth and opioid tolerance and dependence therapy.

According to a further aspect of the invention, the compounds of formula (I) can be used in the treatment or prophylaxis of eating disorders such as anorexia and bulimia; anxiety and stress condition; gastrointestinal disorders including irritable bowel syndrome, and symptoms associated with non-ulcerous dyspepsia and gastro-oesophageal reflux; diseases of the immune system; dysfunctions of the

cardiovascular system; loss of memory, cognitive disorders, motor damage and neurodegeneration due to Alzheimer's disease; senile dementia, Parkinson's disease or other neurodegenerative pathologies; infarct; epilepsy; altered diuresis and sodium excretion; syndrome of inappropriate anti-diuretic hormone secretion (SIADH); adult respiratory distress syndrome (ARDS); congestive cardiac insufficiency; cirrhosis with ascites; sexual dysfunctions including impotence and frigidity; and altered pulmonary function, including chronic obstructive pulmonary disease.

These compounds can also be useful in the treatment or prophylaxis of cough; asthma; depression; drug abuse such as alcohol abuse; dementia such as vascular dementia and dementia associated with AIDS; metabolic disorders such as obesity; pathologies associated with alterations of arterial pressure, and for water homeostasis and sodium excretion.

The compounds of the invention are therefore useful in the therapy and prophylaxis of all those illnesses dependent on modulation of the ORL-1 receptor, such as the aforestated.

In said formula (I),

R and R^0 are preferably, hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy; more preferably, R and R^0 are hydrogen, chlorine, fluorine, methyl, methoxy.

R^1 is preferably hydrogen, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkinyl, arylC_{1-6}alkyl, (C_{3-7}cycloalkyl)alkyl, hydroxyC_{1-6}alkyl, CO-aryl, SO_2-aryl; more preferably, $R^1$is hydrogen, methyl, n-propyl, isopentyl, allyl, 2-hydroxyethyl, cyclopropylmethyl, cyclohexylmethyl, benzyl, fluorobenzyl, chlorobenzyl, bromobenzyl, methoxybenzyl, methylbenzyl, *t*-butylbenzyl, trifluoromethylbenzyl, diphenylmethyl, phenoxyethyl, 2-naphthylmethyl, benzoyl, benzenesulfonyl.

R^2 is preferably aryl, heteroaryl, arylC_{1-6}alkyl; more preferably, R^2 is phenyl, chlorophenyl, methoxyphenyl, fluorophenyl, 2-furyl, 2-thienyl, 2-pyridyl, benzyl.

R^3 and R^4 are preferably hydrogen, halogen, C_{1-6}alkyl, perhaloC_{1-6}alkyl, C_{1-6}alkoxy; more preferably, R^3 and R^4 are hydrogen, chlorine, fluorine, bromine, methyl, methoxy, trifluoromethyl.

The term "aryl" as used herein includes the C_{5-10}aryl groups, in particular phenyl and naphthyl. The C_{1-6}alkyl groups can be linear or branched and are preferably

C_{1-2}alkyl groups, more preferably methyl. The term "halogen" includes the iodine, chlorine, bromine and fluorine groups, especially chlorine, fluorine and bromine. The term "heteroaryl" includes saturated and unsaturated heterocyclic rings.

Specific compounds of formula (I) according to the present invention (of which each also comprises the corresponding salts such as hydrochloride or trifluorineacetate), are the following:

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1H-indole;

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-methyl-1H-indole;

2-(4-chloro-phenyl)-3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;

2-phenyl-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;

3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;

2-phenyl-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole;

2-(2-chloro-phenyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1H-indole;

2-(2-chloro-phenyl)-3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;

2-(2-chloro-phenyl)-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;

2-(2-chloro-phenyl)-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole;

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-(2-methoxy-phenyl)-1H-indole;

3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-2-(2-methoxy-phenyl)-1H-indole;

2-(2-methoxy-phenyl)-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;

2-(2-methoxy-phenyl)-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole;

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-(3-methoxy-phenyl)-1H-indole;

3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-2-(3-methoxy-phenyl)-1H-indole;

2-(3-methoxy-phenyl)-3-[4-(2-trifliuoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;

2-(3-methoxy-phenyl)-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole;

2-(4-chloro-phenyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1H-indole;

2-(4-chloro-phenyl)-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;

2-(4-chloro-phenyl)-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole;

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-(4-fluoro-phenyl)-1H-indole;

3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-2-(4-fluoro-phenyl)-1H-indole;

2-(4-fluoro-phenyl)-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;
2-(4-fluoro-phenyl)-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-furan-2-yl-1H-indole;
3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-2-furan-2-yl-1H-indole;
2-furan-2-yl-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;
2-furan-2-yl-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-pyridin-2-yl-1H-indole;
3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-2-pyridin-2-yl-1H-indole;
2-pyridin-2-yl-3-[4-(2-difluoro-phenyl)-piperidin-1-ylmethyl]-1H-indole;
3-(4-phenyl-piperidin-1-ylmethyl)-2-pyridin-2-yl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-thiophen-2-yl-1H-indole;
3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-2-thiophen-2-yl-1H-indole;
2-thiophen-2-yl-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;
3-(4-phenyl-piperidin-1-ylmethyl)-2-thiophen-2-yl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-furan-2-yl-1H-indole;
2-benzyl-3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;
2-benzyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1H-indole;
3-[4-(4-methoxy-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(2 fluoro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(3-fluoro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(4-fluoro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
2-phenyl-3-[4-(4-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;
3-[4-(2-chloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(3-chloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(4-chloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
2-phenyl-3-[4-o-tolyl-piperidin-1-ylmethyl]-1H-indole;
3-[4-(2,3-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(2-bromo-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(2,5-dimethyl-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(2,6-difluoro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(3-bromo-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(2-methoxy-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;

1-benzyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1-propyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-methyl-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(2-hydroxyethyl)-2-phenyl-1H-indole;
1-(4-tert-butyl-benzyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(3-methyl-butyl)-2-phenyl-1H-indole;
1-cyclopropylmethyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(3-methoxy-benzyl)-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(2-methyl-benzyl)-2-phenyl-1H-indole;
1-cyclohexylmethyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(4-methyl-benzyl)-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(4-fluoro-benzyl)-2-phenyl-1H-indole;
1-(3-chloro-benzyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
1-(2-chloro-benzyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
1-(4-chloro-benzyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
1-allyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1-prop-2-inyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(2-methoxy-benzyl)-2-phenyl-1H-indole;

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(4-methoxy-benzyl)-2-phenyl-1H-indole;

1-(4-bromo-benzyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;

1-diphenyl-4-ylmethyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-naphthalen-2-ylmethyl-2-phenyl-1H-indole;

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(2-phenoxy-ethyl)-2-phenyl-1H-indole;

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(3-methyl-benzyl)-2-phenyl-1H-indole;

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(2-fluoro-benzyl)-2-phenyl-1H-indole;

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(3-fluoro-benzyl)-2-phenyl-1H-indole;

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1-(2-trifluoromethyl-benzyl)-1H-indole;

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1-(3-trifluoromethyl-benzyl)-1H-indole;

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1-(4-trifluoromethyl-benzyl)-1H-indole;

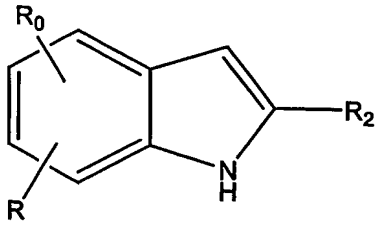
1-benzenesulfonyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;

1-benzoyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole.

The invention also relates to the therapeutic use of a group of compounds of formula (IA): this formula is equal to formula (I), with the only difference that the meanings for R^2 also include hydrogen and C_{1-6}alkyl.

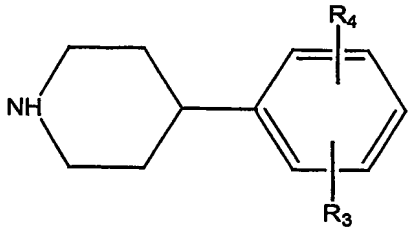
The present invention also provides processes for preparing the compounds of formula (I).

The compounds of formula (I) in which **R1 is hydrogen**, can be obtained as follows: a compound of formula (II)



(II)

in which R, R0 and R2 have the meanings given for formula (I), is functionalised in position 3 by reaction with formaldehyde and a compound of formula (III)

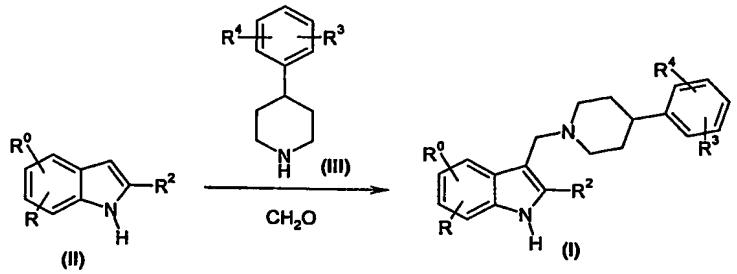


(III)

where R3 and R4 are as defined for formula (I), thus obtaining compounds of formula (I) in which R1 is hydrogen.

The functionalization reaction is preferably a Mannich reaction, as described in standard reference texts of synthesis methodologies such as J.March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience. In particular, the compounds of formula (I) can be prepared in accordance with scheme 1, starting from compounds of formula(I), formaldehyde and amines of formula (III).

Scheme 1



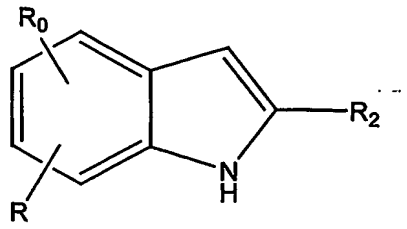
In a typical procedure, an amine of formula (III) is dissolved in a suitable solvent, such as for example methanol or dioxane or a mixture of both, to which solution aqueous formaldehyde and acetic acid are added. After a suitable time, typically between 5 min and 1 h, there is added to the preceding solution a solution of an indole of formula (II) in a suitable solvent, such as for example methanol or dioxane or a mixture of both, while maintaining the temperature of the resultant solution generally between 0°C and ambient temperature. The reaction mixture is stirred for a suitable time, typically between 1 h and 20 h, after which it is processed by known methods.

Two preferred processing procedures are here indicated as procedure A and procedure B.

In procedure A, water is added to the reaction mixture followed by a solution of a suitable base, such as aqueous ammonium hydroxide, until basic pH is reached, after which it is extracted with a suitable organic solvent such as ethyl acetate. The organic phase is collected and dried with, for example, sodium sulfate, and the solvent is removed by evaporation. The crude product can be purified, if necessary, by conventional purification methods such as flash chromatography, trituration, crystallization or preparative HPLC.

In procedure B, the reaction mixture is poured onto an acid resin cartridge and eluted with a suitable solvent, such as for example dichloromethane or methanol, to remove non-basic impurities, and then with a solution of a suitable base in a suitable organic solvent such as, for example, a methanolic ammonia solution, to recover the desired compound of formula (I). The solvent is removed by evaporation and the crude product can be purified, if necessary, by conventional purification methods such as flash chromatography, trituration, crystallization or preparative HPLC.

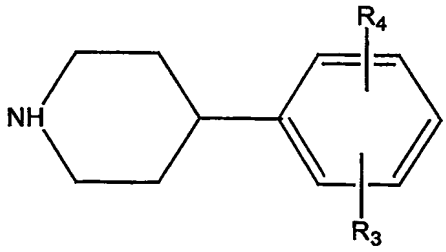
The compounds of formula (I) in which **R1 is different from hydrogen**, can be obtained as follows: a compound of formula (II)



(II)

wherein R1, R0 and R2 have the meanings given for formula (I), is treated in accordance with the two following steps, which can take place in any order:

a) reaction with formaldehyde and a compound of formula (III)



(III)

where R3 and R4 are as defined for formula (I),

b) reaction with a compound of formula R1-X, in which R1 is as defined in formula (I) and X is a suitable leaving group,

thus obtaining the compounds of formula (I).

If the steps are carried out in the order (a) → (b), the compound of formula (II) is firstly functionalized in position 3 by reaction with formaldehyde and the compound of formula (III); the 3-functionalized intermediate obtained is then N-alkylated in position 1 of the indole ring by treatment with the compound R1-X, to obtain the final compound of formula (I).

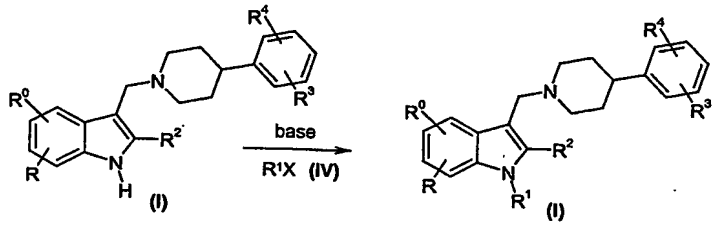
If the steps are carried out in the reverse order (b) → (a), the compound of formula (II) is firstly N-alkylated in position 1 of the indole ring by reaction with the

compound R1-X; the N-alkylated intermediate obtained is then 3-functionalized by reaction with formaldehyde and the compound of formula (III), to obtain the final compound of formula (I).

Step (a) (3-functionalization) is effected preferably by the Mannlich reaction, in the previously detailed manner.

Step (b) is a nucleophilic reaction which can be effected by commonly known methods; in particular it is effected by reacting the compound of formula (II) (or, as illustrated in the following Scheme 2, its 3-substituted derivative resulting from step (a)) with a strong base and then treating the resultant indolyl anion with a suitable alkylating/acylating agent of formula (IV).

Scheme 2



In a typical procedure, a suitable base such as sodium hydride, is added under an inert atmosphere, typically of argon or nitrogen, to a solution of a compound of formula (I) in a suitable anhydrous solvent, such as dimethylformamide, at a suitable temperature, typically between 0°C and ambient temperature. After a suitable time, typically between 15 min and 1 h, a suitable alkyl or acyl halide of formula (IV) is added to the reaction mixture, either as such or dissolved in a suitable anhydrous solvent such as dimethylformamide; if necessary, further additions of alkyl or acyl halide can be made. The resultant reaction mixture is stirred at a suitable temperature, typically ambient temperature, for a suitable time, typically between 1 h and 20 h. The procedure can be carried out by known methods. Two preferred working procedures are here indicated as procedure A and procedure B.

In procedure A, water is added to the reaction mixture, which is then extracted with a suitable organic solvent such as diethylether. The organic phase is collected and dried with, for example, sodium sulfate, and the solvent is removed

by evaporation. The crude product can be purified, if necessary, by conventional purification methods such as flash chromatography, trituration, crystallization and preparative HPLC.

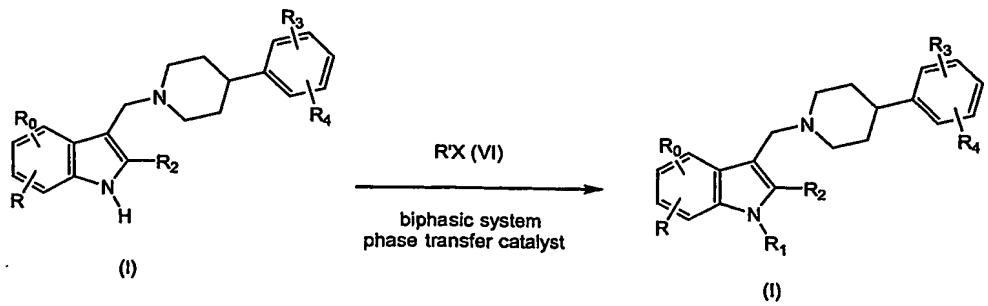
In working procedure B, water is added to the reaction mixture, which is then filtered through a suitable water retention filter, eluting with a suitable solvent such as ethyl acetate. The resultant solution can be concentrated, if necessary, and then poured onto an acid resin cartridge and eluted with a suitable solvent, such as methanol, to remove non-basic impurities, and then with a solution of a suitable base in a suitable organic solvent such as a methanolic solution of ammonia, to recover the desired compound of formula (I). The solvent is removed by evaporation and the crude product can be purified, if necessary, by conventional purification methods such as flash chromatography, trituration, crystallization and preparative HPLC.

The compounds of formula (II) are known or commercially available, or can be prepared by procedures described in standard reference texts of synthesis methodologies, such as *J. March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience.*

The compounds of formula (III) are known or commercially available, or can be prepared by the procedures described in WO 01/83454.

Alternatively, step (b) can be effected by reacting the compound of formula (II) (or, as illustrated in scheme 3, its 3-substituted derivative resulting from step (a)) with a suitable alkylating/acylating agent of formula (IV), under phase transfer conditions, as described in *W.E. Keller, Phase-Transfer Reactions, Vols. 1 e 2, 1986, Georg Thieme Verlag.*

Scheme 3



In a typical procedure, a compound of formula (I) is dissolved in a suitable biphasic system, typically a 1:1 mixture of toluene and an aqueous solution of sodium hydroxide; a suitable phase-transfer catalyst, such as Aliquat® 336 is then added. After a suitable time, typically between 10 min and 1 h, a suitable alkyl- or acyl halide of formula (IV) is added to the reaction mixture; if necessary, further additions of alkyl- or acyl halide can be made. The reaction mixture is stirred vigorously at a suitable temperature, typically ambient temperature, for a suitable time, typically from 5h to 20 h, then filtered through a suitable water retention filter, eluting with a suitable solvent such as ethyl acetate. The solvent is removed by evaporation and the crude product can be purified, if necessary, by conventional purification methods such as flash chromatography, trituration, crystallization and preparative HPLC.

The compounds of formula (IV), for example alkylating/acylating agents, used in step (b), are known or commercially available, or can be prepared by procedures described in standard reference texts of synthesis methodologies such as *J. March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience.*

The compounds of formula (I) of the invention can be prepared in the form of salts or hydrates. Suitable salts are pharmaceutically acceptable salts. Suitable hydrates are pharmaceutically acceptable hydrates.

An effective quantity of compound of the invention depends on factors such as the nature or seriousness of the illness or illnesses to be treated and on the weight of the patient. In all cases a unit dose normally contains from 0.1 to 50 mg, for example from 0.5 to 10 mg, of the compound. Unit doses are normally administered one or more times per day, for example, 2, 3 or 4 times a day, in particular from 1 to 3 times per day, so that the total daily dose is normally, for an adult of 70 kg, between 0.1 and 50 mg, for example between 0.1 and 5 mg, i.e. in the approximate range of 0.001 to 1 mg/kg/day, in particular between 0.005 and 0.2 mg/kg/day. For oral or parenteral administration, it is highly preferred that the compound be administered in the form of unit dose composition for example, in the form of unit dose oral or parenteral composition.

These compositions are prepared by mixing and are suitably adapted to oral or

parenteral administration, and as such can be in the form of tablets, capsules, oral preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible liquid solutions, suspensions or suppositories.

Tablets and capsules for oral administration are normally presented in unit dose form, and contain conventional excipients such as binders, fillers, diluents, compressing agents, lubricants, detergents, disintegrants, colorants, aromas and wetting agents. The tablets can be covered by methods well known in the art.

Suitable fillers include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium glycolate starch. Suitable lubricants include, for example, magnesium stearate. Suitable wetting agents include sodium laurylsulfate.

These solid oral compositions can be prepared by conventional methods of mixing, filling or compression. The mixing operations can be repeated to disperse the active component in compositions containing large quantities of fillers. These operations are conventional.

Oral liquid preparations can be in the form, for example, of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or can be presented as a dry product for reconstitution with water or with a suitable carrier before use. These liquid preparations can contain conventional additives such as suspending agents, for example sorbitol, syrup, methylcellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous carriers (which can include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine esters, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired, conventional aromas or colorants.

Oral formulations also include conventional slow-release formulations, such as tablets or granules having an enteric coating.

For parenteral administration, fluid dose units can be prepared, containing the compound and a sterile carrier. The compound, depending on the carrier and the concentration, can be suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a carrier and sterilizing by means of a

filter, before filling suitable vials or ampoules and sealing. Advantageously, adjuvants such as local anaesthetics, preservatives and buffer agents can also be dissolved in the carrier. To increase stability, the composition can be frozen after filling the vial and removing the water under vacuum. Parenteral suspensions are prepared substantially in the same manner, with the difference that the compound can be suspended in the carrier instead of dissolved, and be sterilized by exposure to ethylene oxide before suspension in the sterile carrier. Advantageously, a surfactant or a wetting agent can be included in the composition to facilitate uniform distribution of the compound of the invention.

As in common practise, the compositions are normally accompanied by written or printed instructions, for use in the treatment in question.

Consequently, another aspect of the present invention also provides a pharmaceutical composition comprising a compound of formula I, or a pharmaceutically suitable salt or hydrate thereof, and a pharmaceutically acceptable carrier.

The invention will now be illustrated by means of the following non-limiting examples.

Example 1

3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole hydrochloride

1.17 g (5.1 mmol) of 4-(2,6-dichloro-phenyl)-piperidine are dissolved in 4 ml of dooxane to which 4 ml of glacial acetic acid and 0.41 ml (5.1 mmol) of a 37% aqueous formaldehyde solution are added, followed by a solution of 893 ml (4.62 mmol) of 2-phenyl-1H-indole in 8 ml of dioxane. The reaction mixture is stirred for 3 h at ambient temperature, then water is added followed by concentrated NH_4OH until the pH is basic. The reaction mixture is extracted with AcOEt, the organic phase is dried with Na_2SO_4 and the solvent removed under vacuum, to obtain 2 g of crude product. 1 g of free base is dissolved in CH_2Cl_2, the solution is adjusted to acid pH with Et_2O/HCl and the solvent is removed under vacuum. The resultant solid is triturated with Et_2O, filtered off and dried, to obtain 1 g of the final compound as white solid.

M.P. = 169-171°C. IR (KBr, cm^{-1}) = 3429, 2370, 1435. NMR (free base, 300 MHz,

$CDCl_3$, δ ppm): 8.19 (s br, 1H); 7.91-7.81 (m, 3H); 7.49 (dd, 2H); 7.39 (d, 2H); 7.29-7.12 (m, 4H); 7.01 (dd, 1H); 3.75 (s, 2H); 3.52 (tt, 1H); 3.12 (m, 2H); 2.63 (dq, 2H); 2.17 (dq, 2H); 1.53 (m, 2H). MS (m/z): 435 (MH^+).

The compounds described in Example 2 and Example 3 were obtained following the procedure described in Example 1.

Example 2

3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-1H-indole hydrochloride

M.P. = 189-190°C. NMR (free base, 300 MHz, $CDCl_3$, δ ppm): 8.10 (s br, 1H); 7.77 (d,1H); 7.38 (d, 1H); 7.27-7.11 (m, 5H); 7.01 (dd, 1H); 3.80 (s, 2H); 3.53-3.40 (m, 1H); 3.13 (m, 2H); 2.67 (dq, 2H); 2.15 (dt, 2H); 1.64-1.49 (m, 2H). MS (m/z): 358 ($M^{+\cdot}$); 228; 194; 130.

Example 3

3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-2-methyl-1H-indole

M.P. = 168-170°C. IR (KBr, cm^{-1}) = 3401, 2904, 1432. NMR (300 MHz, $CDCl_3$, δ ppm): 7.80 (s br, 1H); 7.69 (m, 1H); 7.31-7.19 (m, 3H); 7.15-7.07 (m, 2H); 7.01 (dd, 1H); 3.73 (s, 2H); 3.45 (tt, 1H); 3.08 (m, 2H); 2.71-2.55 (m, 2H); 2.46 (s, 3H); 2.13 (m, 2H); 1.51 (m, 2H). MS (m/z): 372 ($M^{+\cdot}$); 230; 228; 144; 143.

Example 4

2-(4-Chloro-phenyl)-3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole

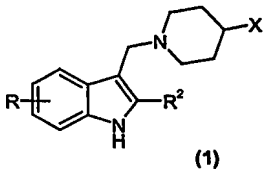
0.021 ml (0.278 mmol) of CH_2O (37% aqueous solution) and 0.017 ml (0.304 mmol) of glacial AcOH are added at ambient temperature to a solution of 48 mg (0.253 mmol) of 4-(2,6-dimethyl-phenyl)-piperidine in 1 ml of an MeOH:dioxane (8:2) mixture. After stirring for 20 minutes, a solution of 63 mg (0.326 mmol) of 2-(4-chloro-phenyl)-1H-indole in 2.5 ml of MeOH:dioxane (8:2) mixture is added, and the resultant mixture is stirred overnight at ambient temperature. The reaction mixture is poured onto an SCX cartridge and eluted with 24 ml of CH_2Cl_2 and 36 ml of MeOH to remove the excess starting material, then with 18 ml of a 3% methanolic ammonia solution to recover the final compound. The solvent is removed under vacuum, to obtain 100 mg of final compound as white solid.

MS (m/z): 429 (MH^+).

The compounds of formula (I) described in Table 1 were obtained by the

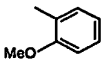
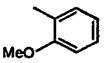
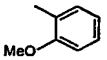
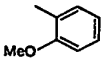
procedure described in Example 4.

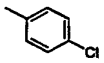
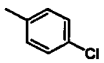
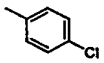
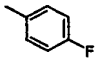
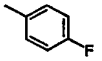
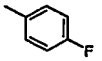
Table 1

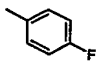


(1)

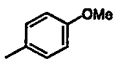
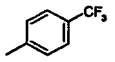
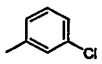
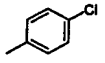
Ex. No.	R	R^2	X	MS (m/z)	Name
5	H			435 (MH^+)	2-Phenyl-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole
6	H			395 (MH^+)	3-[4-(2,6-Dimethyl-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole
7	H			367 (MH^+)	2-Phenyl-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole
8	H			469 (MH^+)	2-(2-Chloro-phenyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1H-indole
9	H			429 (MH^+)	2-(2-Chloro-phenyl)-3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole
10	H			469 (MH^+)	2-(2-Chloro-phenyl)-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole

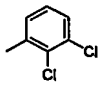
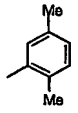
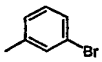
11	H			401 (MH^+)	2-(2-Chloro-phenyl)-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole
12	H			465 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-2-(2-methoxy-phenyl)-1H-indole
13	H			425 (MH^+)	3-[4-(2,6-Dimethyl-phenyl)-piperidin-1-ylmethyl]-2-(2-methoxy-phenyl)-1H-indole
14	H			46 (MH^+)	2-(2-Methoxy-phenyl)-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole
15	H			397 (MH^+)	2-(2-Methoxy-phenyl)-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole
16	H			465 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-2-(3-methoxy-phenyl)-1H-indole
17	H			425 (MH^+)	3-[4-(2,6-Dimethyl-phenyl)-piperidin-1-ylmethyl]-2-(3-methoxy-phenyl)-1H-indole

18	H			465 (MH^+)	2-(3-Methoxy-phenyl)-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole
19	H			397 (MH^+)	2-(3-Methoxy-phenyl)-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole
20	H			469 (MH^+)	2-(4-Chloro-phenyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1H-indole
21	H			469 (MH^+)	2-(4-Chloro-phenyl)-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole
22	H			401 (MH^+)	2-(4-Chloro-phenyl)-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole
23	H			453 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-2-(4-fluoro-phenyl)-1H-indole
24	H			413 (MH^+)	3-[4-(2,6-Dimethyl-phenyl)-piperidin-1-ylmethyl]-2-(4-fluoro-phenyl)-1H-indole
25	H			453 (MH^+)	2-(4-Fluoro-phenyl)-3-[4-(2-trifluoromethyl-

					phenyl)-piperidin-1-ylmethyl]-1H-indole
26	H			385 (MH^+)	2-(4-Fluoro-phenyl)-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole
27	H			425 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-2-furan-2-yl-1H-indole
28	H			385 (MH^+)	3-[4-(2,6-Dimethyl-phenyl)-piperidin-1-ylmethyl]-2-furan-2-yl-1H-indole
29	H			425 (MH^+)	2-Furan-2-yl-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole
30	H			357 (MH^+)	2-Furan-2-yl-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole
31	H			436 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-2-Pyridin-2-yl-1H-indole
32	H			396 (MH^+)	3-[4-(2,6-Dimethyl-phenyl)-piperidin-1-ylmethyl]-2-Pyridin-2-yl-1H-indole
33	H			436 (MH^+)	2-Pyridin-2-yl-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-

					ylmethyl]-1H-indole
34	H			368 (MH^+)	3-(4-Phenyl-piperidin-1-ylmethyl)-2-Pyridin-2-yl-1H-indole
35	H			441 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-2-thiophen-2-yl-1H-indole
36	H			401 (MH^+)	3-[4-(2,6-Dimethyl-phenyl)-piperidin-1-ylmethyl]-2-thiophen-2-yl-1H-indole
37	H			441 (MH^+)	2-Thiophen-2-yl-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole
38	H			373 (MH^+)	3-(4-Phenyl-piperidin-1-ylmethyl)-2-thiophen-2-yl-1H-indole
39	H			409 (MH^+)	2-Benzyl-3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole
40	H			449 (MH^+)	2-Benzyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1H-indole

41	H			397 (MH^+)	3-[4-(4-Methoxy-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole
42	H			385 (MH^+)	3-[4-(2-Fluoro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole
43	H			385 (MH^+)	3-[4-(3-Fluoro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole
44	H			385 (MH^+)	3-[4-(4-Fluoro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole
45	H			435 (MH^+)	2-Phenyl-3-[4-(4-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole
46	H			401 (MH^+)	3-[4-(2-Chloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole
47	H			401 (MH^+)	3-[4-(3-Chloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole
48	H			401 (MH^+)	3-[4-(4-Chloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole

49	H			381 (MH^+)	2-Phenyl-3-(4-o-tolil-piperidin-1-ylmethyl)-1H-indole
50	H			445 (MH^+)	3-[4-(2-Bromo-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole
51	H			435 (MH^+)	3-[4-(2,3-Dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole
52	H			395 (MH^+)	3-[4-(2,5-Dimethyl-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole
53	H			403 (MH^+)	3-[4-(2,6-Difluoro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole
54	H			445 (MH^+)	3-[4-(3-Bromo-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole
55	H			397 (MH^+)	3-[4-(2-Methoxy-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole

Example 56

1-Benzyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole hydrochloride

13.2 mg (0.331 mmol) of NaH (60% dispersion in mineral oil) were suspended in

0.75 ml of anhydrous DMF under a nitrogen atmosphere. After cooling to 0°C, a solution of 120 mg (0.276 mmol) of 3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole in 0.75 ml of anhydrous DMF are added dropwise. The reaction mixture is stirred for 30 min, then 0.036 ml (0.304 mmol) of benzyl bromide are added dropwise. The reaction mixture is left to warm to ambient temperature and stirred for 2 h, then cooled to 0°C, water is added followed by conc. NH_4OH and the resultant mixture extracted with Et_2O. The organic phase is dried with Na_2SO_4 and the solvent removed under vacuum, to obtain 122 mg of crude product, which is then dissolved in CH_2Cl_2, the solution is adjusted to acid pH with Et_2O/HCl and the solvent is removed under vacuum. The resultant solid is triturated with hot acetone, filtered off and dried, to obtain 53 mg of the final compound as white solid.

M.P. = 209-210 °C. NMR (free base, 300 MHz, $CDCl_3$, δ ppm): 7.94 (m, 1H); 7.45-7.35 (m, 5H); 7.28-7.14 (m, 9H); 7.00 (dd, 1H); 6.95 (m, 1H); 5.23 (s, 2H); 3.68 (s, 2H); 3.43 (tt, 1H); 3.02 (m, 2H); 2.59 (dq, 2H); 2.04 (dt, 2H); 1.47 (m, 2H). MS (m/z): 525 (MH^+).

The compounds described in examples 57 and 58 were obtained by the procedure described in example 56.

Example 57

3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1-propyl-1H-indole hydrochloride

M.P. = 150-152°C. NMR (free base, 300 MHz, $CDCl_3$, δ ppm): 7.91 (d, 1H); 7.51-7.39 (m, 5H); 7.36 (d, 1H); 7.27-7.19 (m, 3H); 7.15 (dd, 1H); 7.00 (t, 1H); 3.98 (dd, 2H); 3.63 (s, 2H); 3.41 (tt, 1H); 2.98 (m, 2H); 2.56 (dq, 2H); 2.00 (dt, 2H); 1.66 (m, 2H); 1.44 (m, 2H); 0.74 (t, 3H). MS (m/z): 476 ($M^{+\cdot}$); 248; 206; 178.

Example 58

3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-1-methyl-2-phenyl-1H-indole hydrochloride

M.P. = 179-184°C (dec.). NMR (free base, 300 MHz, $CDCl_3$, δ ppm): 7.90 (d, 1H); 7.55-7.40 (m, 5H); 7.35 (d, 1H); 7.29-7.15 (m, 4H); 7.00 (t, 1H); 3.65 (s, 2H); 3.63 (s, 3H); 3.43 (tt, 1H); 3.01 (m, 2H); 2.58 (dq, 2H); 2.05 (dt, 2H); 1.46 (m, 2H). MS (m/z): 448 ($M^{+\cdot}$); 220; 204.

Example 59

3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-1-(2-hydroxyethyl)-2-phenyl-1H-indole hydrochloride

25 mg (0.62 mmol) of NaH (60% dispersion in mineral oil) are suspended in 0.75 ml of anhydrous DMF under a nitrogen atmosphere. After cooling to 0°C, a solution of 150 mg (0.344 mmol) of 3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole in 0.75 ml of anhydrous DMF are added dropwise. The reaction mixture is stirred for 30 min, then 0.093 ml (0.62 mmol) of 2-(2-bromo-ethoxy)-tetrahydro-pyrane are added dropwise. The reaction mixture is left to warm to ambient temperature and stirred for 2 h, then cooled to 0°C, water is added followed by conc. NH_4OH and the resultant mixture extracted with Et_2O. The organic phase is dried with Na_2SO_4 and the solvent removed under vacuum, to obtain 201 mg of crude product, which is dissolved in a mixture of 2 ml of dioxane and 3 ml of 1N HCl and stirred for 1 h at ambient temperature. Conc. NH_4OH is added until the pH is basic, then the reaction mixture is extracted with Et_2O, the organic phase is dried and the solvent removed under vacuum, to obtain 130 mg of crude product which is dissolved in CH_2CL_2, the solution is adjusted to acid pH with Et_2O/HCl and the solvent is removed under vacuum. The resultant solid is crystallized from acetone, filtered off and dried, to obtain 44 mg of the final compound as white solid.

M.P. = 205-206 °C. NMR (free base, 300 MHz, $CDCl_3$, δ ppm): 7.91 (d, 1H); 7.50-7.41 (m, 6H); 7.29-7.14 (m, 4H); 7.00 (dd, 1H); 4.21 (t, 2H); 3.79 (m, 2H); 3.62 (s, 2H); 3.41 (tt, 1H); 2.98 (m, 2H); 2.56 (dq, 2H); 2.01 (dt, 2H); 1.45 (m, 3H). MS (m/z): 478 ($M^{+\cdot}$); 250.

Example 60

1-(4-*tert*-Butyl-benzyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole trifluoroacetate

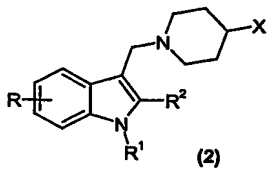
15 mg (0.37 mmol) of NaH (60% dispersion in mineral oil) are added to a solution of 70 mg (0.16 mmol) of 3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole in 0.5 ml of anhydrous DMF are added dropwise. After stirring for 15 min at ambient temperature under an argon atmosphere, 0.1 ml of a 2M solution of 4-*tert*-butyl-benzylbromide in DMF are added; after stirring for 75 min a second

addition of 0.1 ml of a 2M solution of 4-*tert*-butyl-benzylbromide in DMF is made and the resultant mixture is stirred at ambient temperature overnight. The reaction is arrested with a few drops of water, poured onto a Chem-elute water retention cartridge eluted with AcOEt; the resultant solution is concentrated and then poured onto an SCX cartridge and eluted with MeOH to eliminate non-basic impurities and then with a 3% methanolic ammonia solution to recover the final compound. The solvent is removed under vacuum and the resultant crude product is purified by preparative HPLC on a C18 Symmetry column, for gradient elution with a solvent system consisting of water/TFA 99.9:0.1 respectively (A) and CH_3CN/TFA 99.9:0.1 respectively (B) with the following gradient: 25% B (1 min); 25% B→95% B (8 min); 95% B→25% B (1 min), to obtain 27 mg of the final compound.

MS (m/z): 581 (MH^+)

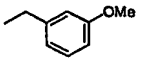
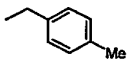
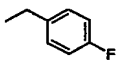
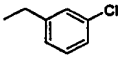
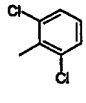
The compounds of formula (2) described in Table 2 were obtained following the procedure described in example 60.

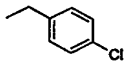
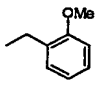
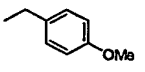
Table 2

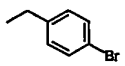
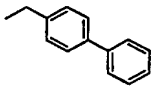
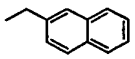
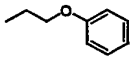
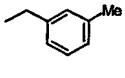
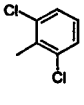


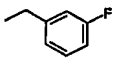
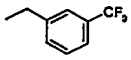
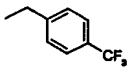
(2)

Ex. No.	R	R^1	R^2	X	MS (m/z)	Name
61	H	$CH_2CH_2CHMe_2$			505 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-1-(3-methyl-butil)-2-phenyl-1H-indole
62	H	Cyclopropyl-methyl			489 (MH^+)	1-Cyclopropylmethyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-

						1H-indole
63	H				555 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-1-(3-methoxy-benzyl)-2-phenyl-1H-indole
64	H				539 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-1-(2-methyl-benzyl)-2-phenyl-1H-indole
65	H				531 (MH^+)	1-Cyclohexylmethyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole
66	H				539 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-1-(4-methyl-benzyl)-2-phenyl-1H-indole
67	H				543 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-1-(4-fluoro-benzyl)-2-phenyl-1H-indole
68	H				559 (MH^+)	1-(3-Chloro-benzyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-

						1H-indole trifluoroacetate
69	H				559 (MH^+)	1-(2-Chloro-benzyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole
70	H				559 (MH^+)	1-(4-Chloro-benzyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole
71	H	Allyl			475 (MH^+)	1-Allyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole
72	H	Propargyl			473 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1-prop-2-inyl-1H-indole
73	H				555 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-1-(2-methoxy-benzyl)-2-phenyl-1H-indole trifluoroacetate
74	H				555 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-1-(4-methoxy-benzyl)-2-phenyl-1H-indole

						trifluoroacetate
75	H				603 (MH^+)	1-(4-Bromo-benzyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole trifluoroacetate
76	H				601 (MH^+)	1-Diphenyl-4-ylmethyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole trifluoroacetate
77	H				575 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-1-naphthalen-2-ylmethyl-2-phenyl-1H-indole trifluoroacetate
78	H				555 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-1-(2-phenoxy-ethyl)-2-phenyl-1H-indole trifluoroacetate
79	H				539 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-1-(3-methyl-benzyl)-2-phenyl-1H-indole trifluoroacetate

80	H				543 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-1-(2-fluoro-benzyl)-2-phenyl-1H-indole trifluoroacetate
81	H				543 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-1-(3-fluoro-benzyl)-2-phenyl-1H-indole trifluoroacetate
82	H				593 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1-(2-trifluoromethyl-benzyl)-1H-indole trifluoroacetate
83	H				593 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1-(3-trifluoromethyl-benzyl)-1H-indole trifluoroacetate
84	H				593 (MH^+)	3-[4-(2,6-Dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1-(4-trifluoromethyl-benzyl)-1H-indole trifluoroacetate

Example 85

1-benzenesulfonyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole trifluoroacetate

100 mg (0.229 mmol) of 3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole are dissolved in 3 ml of a biphasic system consisting of a 1:1 mixture of toluene and 50% aqueous NaOH; two drops of Aliquat® 336 are then added and the system is vigorously for 15 min, then 0.037 ml of benzenesulfonyl chloride are added; two further additions of 0.015 ml of chloride are made during a period of 20 h of agitation at ambient temperature. The resultant mixture is poured onto a Chem-elute cartridge to eliminate the water and eluted with ethyl acetate; the filtrate is evaporated under vacuum and the residue is purified by preparative HPLC on a C18 Symmetry column, for gradient elution with a solvent system consisting of water/TFA 99.9:0.1 respectively (A) and CH_3CN/TFA 99.9:0.1 respectively (B) with the following gradient: 25% B (1 min); 25% B→95% B (8 min); 95% B→25% B (1 min), to obtain 29 mg of the final compound.

MS (m/z): 575 (MH^+).

The compound described in Example 86 was obtained following the procedure described in Example 85.

Example 86

1-Benzoyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole trifluoroacetate

MS (m/z): 539 (MH^+)

Pharmacological tests

Receptor binding studies

The receptor binding studies were carried out on 96-well plates; the incubation medium was Tris HCl pH 7.4 (4°C) containing 100 µg/ml of bacitracine, 4 µg/ml of leupeptin and 2 µg/ml of chymostatin with a final volume of 0.75 ml, using as radioligand [^{3}H]-nociceptin (Amersham, 172 Ci/mmol). The samples were incubated at 25°C for 20 min. and were then filtered off via Whatman GF/B filters pre-treated with 0.2% polyethylenimine. The filters were washed twice with Tris HCl buffer pH 7.4 (4°C). The radioactivity present on the filters was measured using a Canberra Packard 2500 beta counter.

The most potent compounds of formula (I) of the present invention have a bond affinity (Ki) to the receptors ORL-1 in the range of 0.1 to 1000 nm

Preparation of membrane for the GTPγS binding test

The entire process was carried out at 4°C. The buffer used consisted of Tris HCl 10 mM, EDTA 0.1 mM, pH 7.4 (4°C) (T.E.).

The cells removed from the culture flask are centrifuged at low speed to remove the growth medium.

1. Resuspend the pellets (a 175 cm^2 T flask in 0.5-1 ml T.E.).
2. Homogenize the cells using an Ultra-Turrax
3. Centrifuge the homogenate at 1,500 rpm for 10 min at 4°C.
4. Discard the pellets P1
5. Centrifuge the supernatant at 14,000 rpm for 30 min.
6. Discard the supernatant.
7. Resuspend the pellets P2 by suction (microsomal fraction) in 200 ml of T.E. and preserve frozen at -80°C.

To estimate the proteins, dilute the preparation 3 x in T.E. and assay against standard BSA curve 0-2 mg/ml in T.E.. The protein concentration is normally between 1 and 4 mg/ml. The typical yield is 1 mg of proteins per 175 cm^2 T flask at confluence.

Binding tests [^{35}S]-GTPγS

The tests were carried out in a 96-well plate using the method modified by Wieland and Jacobs (*Methods Enzymol.*, 1994, **237**, 3-13). The membranes (10 µg per well) and the SPA granules of wheat germ agglutinin (Amersham Pharmacia) (0.5 mg per well) were pre-mixed in buffer solution (HEPES 20 mM, NaCl 100 mM, $MgCl_2$ 10 mM, pH 7.4, 4°C) and pre-incubated with 10 µM GDP. Increasing concentrations of the compounds to be tested were then incubated with the membrane/granule mixture for 30 min at ambient temperature. 0.3 nM [^{35}S]-GTPγS (1170 Ci/mmol, Amersham) and 30 µM nociceptin were then added. The total volume of the assay is 100 µl per well. The plates are then incubated at ambient temperature for 30 min under agitation and then centrifuged at 1500 g for 5 min. The quantity of [^{35}S]-GTPγS bound to the membranes was determined by a Wallac microbeta 1450-Trilux scintillation counter.

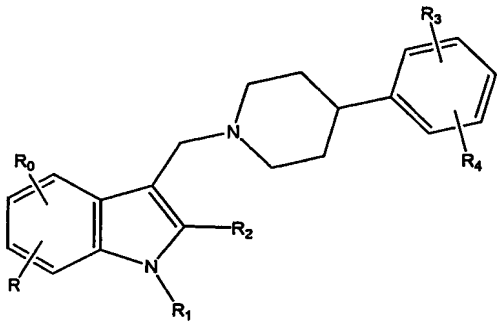
The activity of the compound is evaluated as inhibition of [^{35}S]-GTPγS binding stimulation induced by the agonist (nociceptin).

The pIC50 values are determined as the concentration of compound which causes

a 50% inhibition of nociceptin response.

CLAIMS

1. Compound of formula (I)



(I)

wherein:

R and **R^0** are each independently hydrogen, halogen, C_{1-6}alkyl, perhaloC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aryl,

R^1 is hydrogen, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkinyl, arylC_{1-6}alkyl, heteroarylC_{1-6}alkyl, (C_{3-7}cycloalkyl)alkyl, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, aryloxyC_{1-6}alkyl, CO-aryl, SO_2-aryl where each aryl or heteroaryl can be substituted one or more times by halogen, C_{1-6}alkoxy, C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aryl or perhaloC_{1-6}alkyl,

R^2 is C_{3-7}cycloalkyl, aryl, heteroaryl, arylC_{1-6}alkyl, heteroarylC_{1-6}alkyl, where each aryl or heteroaryl can be substituted one or more times by halogen, C_{1-6}alkoxy, C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aryl or perhaloC_{1-6}alkyl.

R^3 and **R^4** are each independently hydrogen, halogen, C_{1-6}alkyl, perhaloC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aryl.

2. Compound as claimed in claim 1, wherein R and R^0 are hydrogen, chlorine,

fluorine, methyl, methoxy.

3. Compound as claimed in claims 1-2, where R^1 is hydrogen, methyl, n-propyl, isopentyl, allyl, 2-hydroxyethyl, cyclopropylmethyl, cyclohexylmethyl, benzyl, fluorobenzyl, chlorobenzyl, bromobenzyl, methoxybenzyl, methylbenzyl, *t*-butylbenzyl, trifluoromethylbenzyl, diphenylmethyl, phenoxyethyl, 2-naphthylmethyl, benzoyl, benzenesulfonyl.

4. Compound as claimed in claims 1-3, wherein R^2 is phenyl, chlorophenyl, methoxyphenyl, fluorophenyl, 2-furyl, 2-thienyl, 2-pyridyl, benzyl.

5. Compound as claimed in claims 1-4, wherein R^3 and R^4 are hydrogen, chlorine, fluorine, bromine, methyl, methoxy, trifuoromethyl.

6. Compound as claimed in claim 1, chosen from:

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1H-indole;

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-methyl-1H-indole;

2-(4-chloro-phenyl)-3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;

2-phenyl-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;

3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;

2-phenyl-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole;

2-(2-chloro-phenyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1H-indole;

2-(2-chloro-phenyl)-3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;

2-(2-chloro-phenyl)-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;

2-(2-chloro-phenyl)-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole;

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-(2-methoxy-phenyl)-1H-indole;

3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-2-(2-methoxy-phenyl)-1H-indole;

2-(2-methoxy-phenyl)-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;

2-(2-methoxy-phenyl)-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole;

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-(3-methoxy-phenyl)-1H-indole;

3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-2-(3-methoxy-phenyl)-1H-indole;

2-(3-methoxy-phenyl)-3-[4-(2-trifliuoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;

2-(3-methoxy-phenyl)-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole;

2-(4-chloro-phenyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1H-indole;
2-(4-chloro-phenyl)-3-[4-(2-trifliuoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;
2-(4-chloro-phenyl)-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-(4-fluoro-phenyl)-1H-indole;
3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-2-(4-fluoro-phenyl)-1H-indole;
2-(4-fluoro-phenyl)-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;
2-(4-fluoro-phenyl)-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-furan-2-yl-1H-indole;
3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-2-furan-2-yl-1H-indole;
2-furan-2-yl-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;
2-furan-2-yl-3-(4-phenyl-piperidin-1-ylmethyl)-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-pyridin-2-yl-1H-indole;
3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-2-pyridin-2-yl-1H-indole;
2-pyridin-2-yl-3-[4-(2-difluoro-phenyl)-piperidin-1-ylmethyl]-1H-indole;
3-(4-phenyl-piperidin-1-ylmethyl)-2-pyridin-2-yl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-thiophen-2-yl-1H-indole;
3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-2-thiophen-2-yl-1H-indole;
2-thiophen-2-yl-3-[4-(2-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;
3-(4-phenyl-piperidin-1-ylmethyl)-2-thiophen-2-yl-1H-indole;
2-benzyl-3-[4-(2,6-dimethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;
2-benzyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1H-indole;
3-[4-(4-methoxy-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(2 fluoro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(3-fluoro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(4-fluoro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
2-phenyl-3-[4-(4-trifluoromethyl-phenyl)-piperidin-1-ylmethyl]-1H-indole;
3-[4-(2-chloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(3-chloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(4-chloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
2-phenyl-3-[4-o-tolyl-piperidin-1-ylmethyl]-1H-indole;
3-[4-(2,3-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(2-bromo-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;

3-[4-(2,5-dimethyl-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(2,6-difluoro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(3-bromo-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(2-methoxy-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
1-benzyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1-propyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-methyl-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(2-hydroxyethyl)-2-phenyl-1H-indole;
1-(4-*tert*-butyl-benzyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(3-methyl-butyl)-2-phenyl-1H-indole;
1-cyclopropylmethyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(3-methoxy-benzyl)-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(2-methyl-benzyl)-2-phenyl-1H-indole;
1-cyclohexylmethyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(4-methyl-benzyl)-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(4-fluoro-benzyl)-2-phenyl-1H-indole;
1-(3-chloro-benzyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
1-(2-chloro-benzyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
1-(4-chloro-benzyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
1-allyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;

3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1-prop-2-inyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(2-methoxy-benzyl)-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(4-methoxy-benzyl)-2-phenyl-1H-indole;
1-(4-bromo-benzyl)-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
1-diphenyl-4-ylmethyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-naphthalen-2-ylmethyl-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(2-phenoxy-ethyl)-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(3-methyl-benzyl)-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(2-fluoro-benzyl)-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-1-(3-fluoro-benzyl)-2-phenyl-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1-(2-trifluoromethyl-benzyl)-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1-(3-trifluoromethyl-benzyl)-1H-indole;
3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1-(4-trifluoromethyl-benzyl)-1H-indole;
1-benzenesulfonyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole;
1-benzoyl-3-[4-(2,6-dichloro-phenyl)-piperidin-1-ylmethyl]-2-phenyl-1H-indole.

7. Enantiomer of a compound of formula (I) as described in claim 1.

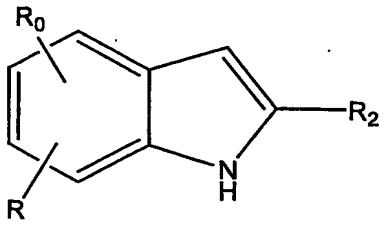
8. Mixture of enantiomers of a compound of formula (I) as described in claim 1, where an enantiomer is present in greater proportion than its antipod.

9. Compound of formula (I) as defined in claim 1, for use as active therapeutic

substance.

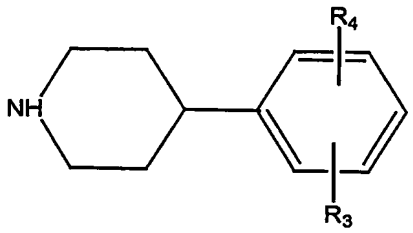
10. Pharmaceutical composition comprising a compound of formula (I) as defined in claim 1, or a pharmaceutically acceptable salt or hydrate thereof, associated with one or more pharmaceutically acceptable excipients.

11. Process for preparing a compound of formula (I) as defined in claim 1, where R1 is hydrogen, comprising the treatment of a compound of formula (II)



(II)

in which R, R0 and R2 have the meanings indicated in claim 1, with formaldehyde and a compound of formula (III)



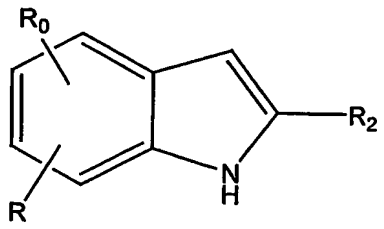
(III)

where R3 and R4 have the meanings indicated in claim 1, thus obtaining compounds of formula (I) in which R1 is hydrogen.

12. Process as claimed in claim 11, wherein the reaction for converting compound (II) to compound (I) is a Mannlich reaction.

13. Process as claimed in claim 12, wherein the Mannlich reaction is carried out in an organic solvent environment, in the presence of formaldehyde and acetic acid.

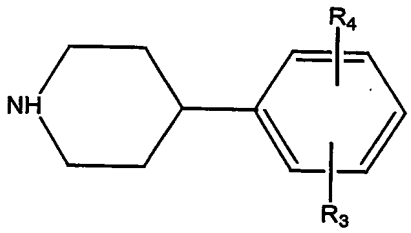
14. Process for preparing a compound of formula (I) as defined in claim 1, where R1 is different from hydrogen, comprising the treatment of a compound of formula (II)



(II)

in which R1, R0 and R2 are as defined in claim 1, in accordance with the following two steps, which can take place in any order:

a) treatment with formaldehyde and a compound of formula (III)



(III)

where R3 and R4 are as defined in claim 1,

b) treatment with a compound of formula R1-X, in which R1 is as defined in claim 1 and X is a suitable leaving group,

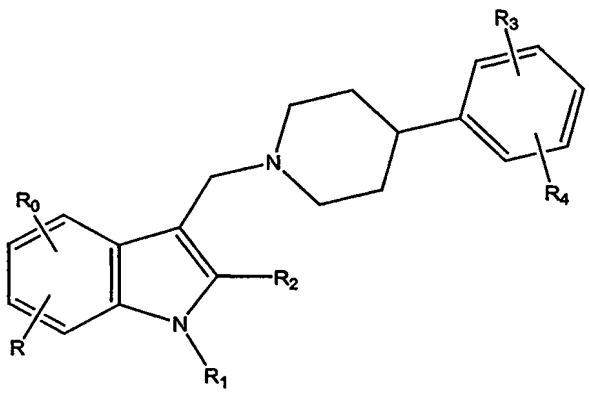
thus obtaining the compounds of formula (I), in which R1 is different from hydrogen.

15. Process as claimed in claim 14, wherein step (a) is effected by a Mannlich reaction.

16. Process as claimed in claim 15, wherein said Mannlich reaction is carried out in an organic solvent environment, in the presence of formaldehyde and acetic acid.

17. Process as claimed in claims 14-16, wherein step (b) takes place in the presence of a strong base, or under phase transfer conditions.

18. Use of a compound of formula (IA)



(IA)

wherein:

R and $\mathbf{R^0}$ are each independently hydrogen, halogen, C_{1-6}alkyl, perhaloC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aryl,

$\mathbf{R^1}$ is hydrogen, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkinyl, arylC_{1-6}alkyl, heteroarylC_{1-6}alkyl, (C_{3-7}cycloalkyl)alkyl, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, aryloxyC_{1-6}alkyl, CO-aryl, SO_2aryl where each aryl or heteroaryl can be substituted one or more times by halogen, C_{1-6}alkoxy, C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aryl or perhaloC_{1-6}alkyl,

$\mathbf{R^2}$ is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, heteroaryl, arylC_{1-6}alkyl, heteroarylC_{1-6}alkyl, where each aryl or heteroaryl can be substituted one or more times by halogen, C_{1-6}alkoxy, C_{1-6}alkyl, hydroxy, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aryl or perhaloC_{1-6}alkyl.

$\mathbf{R^3}$ and $\mathbf{R^4}$ are each independently hydrogen, halogen, C_{1-6}alkyl, perhaloC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)amino, aminoC_{1-6}alkyl, (C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, aryl,

in the preparation of a drug for administration to a human or animal patient for modulating the activity of the ORL-1 receptors.

19. Use as claimed in claim 18, wherein said drug is useful in the prophylaxis and treatment of illnesses dependent on modulation of the ORL-1 receptor.

20. Use as claimed in claims 18-19, wherein said illnesses are chosen from acute pain, chronic neuropathic or inflammatory pain, including post-herpes neuralgia, neuralgia, diabetic neuropathy and post-infarct pain, visceral pain including that associated with irritable bowel syndrome, dysmenorrhea, and hyperreflexia of the bladder, osteoarthritis, back pain, labour pain in childbirth and opioid tolerance and dependence therapy, eating disorders such as anorexia and bulimia, anxiety and stress condition, gastrointestinal disorders including irritable bowel syndrome, and symptoms associated with non-ulcerous dyspepsia and gastro-oesophageal reflux, diseases of the immune system, dysfunctions of the cardiovascular system, loss of memory, cognitive disorders, motor damage and neurodegeneration due to Alzheimer's disease, senile dementia, Parkinson's disease or other neurodegenerative pathologies, infarct, epilepsy, altered diuresis and sodium excretion, syndrome of inappropriate anti-diuretic hormone secretion (SIADH), adult respiratory distress syndrome (ARDS), congestive cardiac insufficiency, cirrhosis with ascites, sexual dysfunctions including impotence and frigidity, altered pulmonary function, including chronic obstructive pulmonary disease, cough, asthma, depression, drug abuse such as alcohol abuse, dementia such as vascular dementia and dementia associated with AIDS, metabolic disorders such as obesity, water homeostasis and sodium excretion, and pathologies associated with alterations of arterial pressure.

(GER/pd)

Milano, July 04, 2003

On behalf of GLAXOSMITHKLINE S.P.A.

The Representative

(signature)

Dr. Gemma Gervasi

NOTARBARTOLO & GERVASI S.p.A.

VERIFIED TRANSLATION

I, Lucia MIGLIORINI, residing in Piazza Belfanti 2 - 20143 Milan (Italy), hereby declare and state that I am knowledgeable of English language and that I made the attached translation of Italian Patent Application No. MI2003A001378 filed on July 04, 2003 from the Italian language into English language and that I believe my attached translation to be accurate, true and correct to the best of my knowledge and ability.

Milano, August 23, 2004

Lucia Migliorini